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Branched-chain amino acids for people with hepatic encephalopathy (Review)

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[Intervention Review]

Branched-chain amino acids for people with hepatic encephalopathy

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ABSTRACT

Background

Hepatic encephalopathy is a brain dysfunction with neurological and psychiatric changes associated with liver insufficiency or portal-systemic shunting. The severity ranges from minor symptoms to coma. A Cochrane systematic review including 11 randomised clinical trials on branched-chain amino acids (BCAA) versus control interventions has evaluated if BCAA may benefit people with hepatic encephalopathy.

Objectives

To evaluate the beneficial and harmful effects of BCAA versus any control intervention for people with hepatic encephalopathy.

Search methods

We identified trials through manual and electronic searches in The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Science Citation Index Expanded and Conference Proceedings Citation Index – Science, and LILACS (May 2017).

Selection criteria

We included randomised clinical trials, irrespective of the bias control, language, or publication status.

Data collection and analysis

The authors independently extracted data based on published reports and collected data from the primary investigators. We changed our primary outcomes in this update of the review to include mortality (all cause), hepatic encephalopathy (number of people without improved manifestations of hepatic encephalopathy), and adverse events. The analyses included random-effects and fixed-effect meta-analyses. We performed subgroup, sensitivity, regression, and trial sequential analyses to evaluate sources of heterogeneity (including intervention, and participant and trial characteristics), bias (using The Cochrane Hepato-Biliary Group method), small-study effects, and the robustness of the results after adjusting for sparse data and multiplicity. We graded the quality of the evidence using the GRADE approach.

Main results

We found 16 randomised clinical trials including 827 participants with hepatic encephalopathy classed as overt (12 trials) or minimal (four trials). Eight trials assessed oral BCAA supplements and seven trials assessed intravenous BCAA. The control groups received placebo/no intervention (two trials), diets (10 trials), lactulose (two trials), or neomycin (two trials). In 15 trials, all participants had cirrhosis. We

classed seven trials as low risk of bias and nine trials as high risk of bias (mainly due to lack of blinding or for-profit funding). In a random-effects meta-analysis of mortality, we found no difference between BCAA and controls (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.69 to 1.11; 760 participants; 15 trials; *moderate quality of evidence*). We found no evidence of small-study effects. Sensitivity analyses of trials with a low risk of bias found no beneficial or detrimental effect of BCAA on mortality. Trial sequential analysis showed that the required information size was not reached, suggesting that additional evidence was needed. BCAA had a beneficial effect on hepatic encephalopathy (RR 0.73, 95% CI 0.61 to 0.88; 827 participants; 16 trials; *high quality of evidence*). We found no small-study effects and confirmed the beneficial effect of BCAA in a sensitivity analysis that only included trials with a low risk of bias (RR 0.71, 95% CI 0.52 to 0.96). The trial sequential analysis showed that firm evidence was reached. In a fixed-effect meta-analysis, we found that BCAA increased the risk of nausea and vomiting (RR 5.56; 2.93 to 10.55; *moderate quality of evidence*). We found no beneficial or detrimental effects of BCAA on nausea or vomiting in a random-effects meta-analysis or on quality of life or nutritional parameters. We did not identify predictors of the intervention effect in the subgroup, sensitivity, or meta-regression analyses. In sensitivity analyses that excluded trials with a lactulose or neomycin control, BCAA had a beneficial effect on hepatic encephalopathy (RR 0.76, 95% CI 0.63 to 0.92). Additional sensitivity analyses found no difference between BCAA and lactulose or neomycin (RR 0.66, 95% CI 0.34 to 1.30).

Authors' conclusions

In this updated review, we included five additional trials. The analyses showed that BCAA had a beneficial effect on hepatic encephalopathy. We found no effect on mortality, quality of life, or nutritional parameters, but we need additional trials to evaluate these outcomes. Likewise, we need additional randomised clinical trials to determine the effect of BCAA compared with interventions such as non-absorbable disaccharides, rifaximin, or other antibiotics.

PLAIN LANGUAGE SUMMARY

Branched-chain amino acids improve symptoms of hepatic encephalopathy

Background

Hepatic encephalopathy is a brain dysfunction associated with liver disease. Cirrhosis, which is a condition where scar tissue (fibrosis) replaces the normal liver tissue, is the most common cause of hepatic encephalopathy. The severity of the symptoms range from minor signs to coma. The minor changes are known as minimal hepatic encephalopathy. Overt hepatic encephalopathy refers to the more severe stages with clinically apparent manifestations such as changes in the level of consciousness or neuropsychiatric abnormalities. Many people with cirrhosis lack amino acids, which are building blocks of proteins. The amino acids with a side-chain (a branch) are known as branched-chain amino acids (BCAA). The BCAA play an important part of the generation muscles and of the signalling chemicals in the brain. These effects may benefit people with hepatic encephalopathy.

Study characteristics

We identified 16 randomised clinical trials (trials where participants are randomly allocated to treatment groups) including 827 participants. The included people had cirrhosis often due to alcoholic liver disease or viral hepatitis (liver infection due to a virus). The trials compared BCAA with placebo (a pretend treatment), no intervention, diets, lactulose (a liquid sugar often used to treat constipation), or neomycin (an antibiotic). The evidence is current to October 2014.

Key results

The analyses found no effect on mortality, but that BCAA had a beneficial effect on symptoms and signs of hepatic encephalopathy. BCAA did not increase the risk of serious adverse events, but was associated with nausea and diarrhoea. When excluding trials on lactulose or neomycin, BCAA had a beneficial effect on hepatic encephalopathy. When analysing trials with a lactulose or neomycin control, we found no beneficial or detrimental effect of BCAA.

Quality of the evidence

We assessed the quality of the evidence to evaluate aspects that can lead to errors in the judgment of intervention effects. We concluded that we had high quality evidence in our analyses about the effect of BCAA on hepatic encephalopathy. We concluded that we had moderate or low quality evidence in the remaining analyses because the number of participants in the trials was too small and the risk of bias (systematic errors) was unclear or high.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Branched-chain amino acids (BCAA) versus control for hepatic encephalopathy

BCAA versus control for hepatic encephalopathy.

Patient or population: people with hepatic encephalopathy.
Settings:
Intervention: BCAA versus control.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	BCAA versus control				
Mortality Clinically Follow-up: 1 to 104 weeks	**Study population**		**RR 0.88** (0.69 to 1.11)	760 (15 studies)	⊕⊕⊕⊖ **moderate**[1]	-
	226 per 1000	**199 per 1000** (156 to 251)				
	Moderate					
	171 per 1000	**150 per 1000** (118 to 190)				
Hepatic encephalopathy Psychometric and clinical assessments Follow-up: 1 to 104 weeks	**Study population**		**RR 0.73** (0.61 to 0.88)	827 (16 studies)	⊕⊕⊕⊕ **high**[2]	-
	633 per 1000	**462 per 1000** (386 to 557)				
	Moderate					
	624 per 1000	**456 per 1000** (381 to 549)				
Nausea and diarrhoea Clinically Follow-up: 1 to 104 weeks	**Study population**		**RR 3.39** (0.7 to 16.46)	945 (5 studies)	⊕⊕⊖⊖ **low**[3]	-
	22 per 1000	**74 per 1000** (15 to 360)				
	Moderate					
	35 per 1000	**119 per 1000**				

		(24 to 576)				
Albumin Laboratory assessment Follow-up: 1 to 104 weeks	-	The mean albumin in the intervention groups was **0.6 higher** (0.9 lower to 2.09 higher)	-	176 (3 studies)	⊕⊕⊖⊖ **low**[4,5]	-
Nitrogen balance Laboratory assessment Follow-up: 1 to 104 weeks	-	The mean nitrogen balance in the intervention groups was **0.81 standard deviations higher** (0.07 to 1.56 higher)	-	108 (3 studies)	⊕⊕⊖⊖ **low**[4,5]	SMD 0.81 (95% CI 0.07 to 1.56)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BCAA: branched-chain amino acids; **CI:** confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The trial sequential analysis showed that additional evidence is needed and that we have not yet reached the required information size.
[2] An analysis of trials with a low risk of bias (RR 0.71; 95% CI 0.52 to 0.96) and trial sequential analysis confirmed the result. No publication bias detected in funnel plots or regression analyses.
[3] Downgraded due to imprecision and lack of trials with a low risk of bias in the overall assessment.
[4] Indirect outcome used as a surrogate estimate of nutritional status.
[5] Due to the small number of trials, we were unable to determine the risk of publication bias.

BACKGROUND

Description of the condition

Hepatic encephalopathy is a brain dysfunction associated with significant liver insufficiency or portal-systemic shunting (Guerit 2009; Randolph 2009; Bajaj 2011). The symptoms include neurological and psychiatric changes and the severity ranges from minor symptoms to coma (Blei 2001). People with minimal hepatic encephalopathy have no clinically overt signs, but have neuropsychiatric deficiencies that are diagnosed through psychometric tests (Amodio 2008). Overt hepatic encephalopathy in people with cirrhosis generally occurs due to an event such as variceal bleeding or infections. Mortality approaches 50% among people who are hospitalised with severe hepatic encephalopathy (Fichet 2009), and 3% to 14% among people diagnosed with minimal hepatic encephalopathy (Marchesini 2003; Muto 2005). Both overt and minimal hepatic encephalopathy are associated with physical symptoms and have a considerable impact on the quality of life (Wein 2004; Bajaj 2008).

Description of the intervention

The three branched-chain amino acids (BCAA) leucine, isoleucine, and valine are essential amino acids with a carbon chain (Holecek 2010). Nutritional supplements containing BCAA can be administered orally or intravenously. The available products also differ in terms of the content as is illustrated in randomised clinical trials on BCAA with products containing different amounts of BCAA (Malaguarnera 2009; Les 2011; Amodio 2014; Roman 2014).

How the intervention might work

The pathogenesis of hepatic encephalopathy is not completely understood. Ammonia plays a central role (Holecek 2014). Most interventions for hepatic encephalopathy are directed against a reduction of ammonia (Wright 2007; Garcia-Martinez 2011). Hyperammonaemia is one of the main causes of decreased levels of BCAA in liver cirrhosis (Holecek 2011). In cirrhosis, BCAA are consumed in skeletal muscle (Dam 2011; Holecek 2013). Biochemically, BCAA supply muscle tissue with carbon skeletons for replenishment of α-ketoglutarate, which may be depleted during hyperammonaemia through enhanced amination to glutamate and, subsequently, amidation of glutamate to glutamine. BCAA and glutamate concentrations in plasma and muscle tissue are reduced in people with cirrhosis and hyperammonaemia, and the removal of ammonia in muscle is proportional to the removal of BCAA in people with cirrhosis. Skeletal muscle is believed to play a key role in ammonia detoxification in people with cirrhosis and several studies have indicated that BCAA enhance this detoxification (Dam 2011; Holecek 2013). However, the effects of BCAA supplements are complex. BCAA supplementation may reduce malnutrition and revert the loss of muscle cell mass that is common in severe liver disease and the breakdown of protein that occurs in people with hepatic encephalopathy (Córdoba 2004; Kachaamy 2011). The increased muscle mass may increase extrahepatic ammonia detoxification (Olde 2002). Glutamine synthetase activity is high in muscle tissue, which promotes detoxification of ammonia to glutamine. BCAA supplementation also increases plasma levels of BCAA and reduce the ratio between aromatic amino acids and BCAA (Holecek 2010). BCAA may further enhance detoxification of ammonia in skeletal muscle by the amidation process for glutamine synthesis (Kawaguchi 2013). The addition of BCAA reduces cerebral efflux of aromatic amino acids across the blood-brain barrier and the imbalance of the synthesis of dopamine, noradrenaline, and serotonin (Bak 2006).

Why it is important to do this review

Cognitive impairment associated with cirrhosis results in larger utilisation of healthcare resources in adults more than any other manifestations of liver disease (Rakoski 2012). Diagnostic tools range from simple scales to sophisticated psychometric tests. The value of the individual tools and the selection of the best diagnostic strategy depend on the clinical situation. Accordingly, investigators in clinical trials on hepatic encephalopathy have used a variety of scales and tests in their assessments of the diagnosis and improved manifestations of hepatic encephalopathy (Egberts 1985; Marchesini 1990; Marchesini 2003; Les 2011). The assessment of clinically relevant improvement in hepatic encephalopathy is an essential outcome, irrespective of the severity of symptoms (Bajaj 2010; Bajaj 2011; AASLD and EASL guideline 2014a; AASLD and EASL guideline 2014b). Based on the available evidence, the 2014 joint guidelines from the American Association for the Study of Liver Diseases (AASLD and EASL guideline 2014a), and the European Association for the Study of the liver (AASLD and EASL guideline 2014b), recommend treatment of any precipitating factors and non-absorbable disaccharides as the initial treatment. The guidelines recommend BCAA as an alternative or additional agent to treat people who do not respond to the initial therapy. Previous meta-analyses of randomised trials and observational studies suggested that the evidence on BCAA supplements is inconclusive due to methodological concerns, small sample sizes, and short follow-up (Tygstrup 1984; Naylor 1989; Gluud 1991; Als-Nielsen 2003; Metcalfe 2014). Subsequent randomised trials are likely to contain important new information (Marchesini 2003; Muto 2005; Les 2011). In particular, systematic reviews on intervention for hepatic encephalopathy found essential information on orally administered BCAA supplements (Gluud 2013a; Gluud 2013b). Therefore, we performed this updated systematic review. In the updated review, we changed the methods and reporting to reflect current guidelines in the Cochrane Hepato-Biliary Group Module (Gluud 2017), the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), and the Methodological Expectations of Cochrane Intervention Reviews (MECIR) guidelines (MECIR 2014).

OBJECTIVES

To evaluate the beneficial and harmful effects of BCAA versus any control intervention for people with hepatic encephalopathy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials irrespective of blinding, publication status, or language in our primary analyses and attempted to identify quasi-randomised and observational studies for the analyses of adverse events.

Types of participants

People with overt or minimal hepatic encephalopathy associated with acute or chronic liver disease (AASLD and EASL guideline

2014a; AASLD and EASL guideline 2014b). The diagnosis could be made based on clinical evaluations (e.g., using standardised scores), psychometric and neurophysiological scores, electroencephalography, or laboratory testing (ammonia). We based the diagnosis on the criteria reported in the individual trials.

Types of interventions

Any form of BCAA, irrespective of dose or duration. People in the control groups could receive placebo, no intervention, diets, non-absorbable disaccharides, antibiotics, or any other intervention with a potential effect on hepatic encephalopathy.

Types of outcome measures

As recommended (Gluud 2017), we included adverse events as our primary outcome measure and changed all outcomes to unwanted events (when possible). We evaluated outcomes at the maximum duration of follow-up.

Primary outcomes

1. Mortality (all-cause).
2. Hepatic encephalopathy (number of people without improved manifestations of hepatic encephalopathy).
3. Adverse events: any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was a congenital anomaly/birth defect, or any medical event that might have jeopardised the person, or required intervention to prevent it (ICH GCP 1997).

Secondary outcomes

1. Quality of life.
2. Markers of nutritional status including albumin and nitrogen balance (the nitrogen input minus the nitrogen output).

Search methods for identification of studies

Electronic searches

We performed the electronic searches in the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, Science Citation Index Expanded and Conference Proceedings Citation Index – Science (Web of Science), and Lilacs (Bireme) (Royle 2003). Appendix 1 displays the search strategies with the time spans of the searches. We did not have access to Chinese, Russian, and Japanese databases, which is a limitation when searching for randomised trials of possible interest to the review. We hope that helped by The CHBG Trials Search Co-ordinator, we will be able to search for further trials also in these databases next time when we update our review.

Searching other resources

The authors conducted manual searches included scanning of reference lists in relevant papers, specialist journals, conference proceedings, and searches in the World Health Organization online trial meta-register (apps.who.int/trialsearch/). We also searched Google Scholar (using the terms 'branched chain amino acids' AND 'cirrhosis* AND random*) and wrote to experts for information about any additional published or unpublished trials.

Data collection and analysis

At least two authors (LG, GD, and GB) independently extracted data from the published trial reports. We wrote to authors of included trials for additional information including data that would allow recalculation of outcomes when necessary. For trials described in more than one record, we used the record with the most complete information (the largest number of participants and events and the longest duration of follow-up).

Selection of studies

We listed trials identified through the electronic and manual searches, selected trials using the criteria described above and listed excluded trials with the reason for exclusion (see Characteristics of excluded studies).

Data extraction and management

We extracted the following data:

- participant characteristics: inclusion criteria, mean age, proportion of men, and type of underlying liver disease;
- intervention characteristics: type, dose, and duration of interventions;
- trial characteristics: setting (hospital or outpatient), number of clinical sites, country of origin, patient inclusion period, and funding.

Assessment of risk of bias in included studies

Authors independently assessed the risk of bias in included trials based on individual domains according to the Cochrane Hepato-Biliary Group Module (Gluud 2017). We classed each domain as having a low, uncertain, or high risk of bias based on the definitions described below. As recommended, we included an analysis that combined all domains and categorised trials as low risk of bias if none of the domains were classed as high or unclear risk of bias.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the method of sequence generation was not specified.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g., if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants.

Blinding of participants, personnel, and outcome assessors

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding. We defined the outcome all-cause mortality and laboratory assessments as unlikely to be influenced by lack of blinding (Savovic 2012).
- Unclear risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding.

Blinding of outcome assessors

- Low risk of bias: outcome assessment was carried out blinded for all relevant outcomes, and the method of blinding was described, so that knowledge of allocation was prevented.
- Unclear risk of bias: blinding of outcome assessment was not described, or the outcome assessment was described as blinded, but the method of blinding was not described, so that knowledge of allocation was possible.
- High risk of bias: outcome assessment was not blinded, so that the allocation was known to outcome assessors.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk: the trial reported mortality and hepatic encephalopathy. If the original trial protocol was available, the outcomes should have been those called for in that protocol.
- Unclear risk: it was unclear whether data on the pre-defined outcomes were recorded or not.
- High risk: one or more of the pre-defined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship was provided.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other bias including vested interests and medicinal dosing problems that could put it at risk of bias.
- Unclear risk of bias: there was insufficient information to determine if the trial was free of other biases.
- High risk of bias: there were factors in the trial that could put it at risk of bias: for example, funding from a for-profit organisation or the administration of inappropriate treatment was given to the controls (such as an inappropriate dose).

Measures of treatment effect

We used risk ratio (RR) for dichotomous outcomes and standardised mean differences (SMD) for continuous outcomes, both with 95% confidence intervals (CI).

Unit of analysis issues

For cross-over trials, we only used data from the first treatment period. For trials with more than one control group (e.g., trials with two different control diets), we combined data from the two control groups.

Dealing with missing data

We gathered data to allow intention-to-treat analyses. Our analyses included data on all participants randomised, irrespective of compliance, protocol violations, or follow-up. We used simple imputation to evaluate the potential influence of missing data (Higgins 2008). The analyses included missing values counted as failures or successes using the following strategies:

- all participants with missing data counted as failures;
- participants with missing outcome data in the BCAA arm counted as failures and in the control arm as successes.

Assessment of heterogeneity

We expressed heterogeneity as I^2 values using the thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and greater than 80% (considerable).

Assessment of reporting biases

For meta-analyses with at least 10 trials, we assessed reporting biases and other dissemination biases based on analyses of small-study effects (Higgins 2011b) using the Harbord modified test for dichotomous outcomes and Egger tests for continuous outcomes (Egger 1997; Harbord 2006). We also attempted to obtain trial protocols to compare reported outcome measures in the protocol and published trial. The Harbord test regresses Z/sqrt(V) against sqrt(V), where Z was the efficient score and V was Fisher's information (the variance of Z under the null hypothesis). The Egger test performs a linear regression of the intervention effect estimates on their standard errors, weighing by 1/(variance of the intervention effect estimate). We reported the result as P values.

Data synthesis

We performed our analyses using Review Manager 5 (RevMan 2014), STATA (Stata 13), and trial sequential analysis (Thorlund 2011; TSA 2011).

Meta-analysis

We performed random-effects and fixed-effect meta-analyses, but only reported the results of the fixed-effect meta-analyses if the result of the two models differed.

Trial sequential analysis

We performed a trial sequential analysis for the outcome measures mortality and hepatic encephalopathy using random-effects models with alpha set to 5%, power to 80%, and model-based heterogeneity (Wetterslev 2008; Higgins 2011b). We defined the required information size as the number of participants needed to detect or reject an intervention effect estimate based on the event proportion in the control group, the observed relative risk reduction (RRR), and the diversity of the meta-analysis (Wetterslev 2009). We constructed trial sequential monitoring boundaries (the inward sloping red lines) based on the required information size and defined firm evidence as being established if the Z-curve (the result of the cumulative meta-analysis) crossed the monitoring boundary and the required information size (the vertical red line at the end of the graph). In the analysis of mortality, we set alpha to 5%, power to 80%, control group event rate to 25%, RRR to 5%, and heterogeneity correction to 17%. In the analysis of hepatic encephalopathy, we set alpha to 5%, power to 80%, control group event rate to 63%, RRR to 45%, and heterogeneity correction to 47%. To account for the risk of overestimation of intervention effects due to bias (Savovic 2012), we also conducted the analysis with the control group event rate set to 45% and RRR set to 35% for hepatic encephalopathy.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses (reported using the P value based on test for subgroup differences):

- type of hepatic encephalopathy (overt or minimal);
- mode of administration (oral or intravenous);
- type of control group (e.g., placebo/no intervention, diets, non-absorbable disaccharides or antibiotics).

We used univariable meta-regression analyses to evaluate the potential influence of continuous trial characteristics (e.g., the dose of BCAA and the duration of therapy) for meta-analyses with at least 10 trials.

Sensitivity analysis

To evaluate the robustness of the overall results, we repeated our analyses:

- including only trials with a low risk of bias based on individual domains;
- comparing trials published in abstract form or as full-paper article;
- comparing the re-calculated outcomes based on individual participant data or published data.

Exploratory (post-hoc) analyses

Based on peer-review comments, we performed sensitivity analysis in which we excluded:

- trials that included people with or without cirrhosis;
- trials with a lactulose or neomycin control group;
- trials with a placebo/no intervention or diet control group (i.e., only included trials with a lactulose or neomycin control group).

We also performed univariable and multivariable random-effects meta-regression analyses to evaluate predictors of heterogeneity including characteristics of the experimental intervention (the dose, duration, and mode of administration), the control intervention (type of control group), and participant characteristics (proportion of men, mean age, proportion of participants with cirrhosis, and type of hepatic encephalopathy).

'Summary of findings' tables

We included a Summary of findings for the main comparison (Guyatt 2008) prepared using GRADE software (GRADEpro) with information on the results of our primary outcomes in relation to the quality of the evidence based on the risk of heterogeneity, indirectness, imprecision, risk of bias, and publication bias.

RESULTS

Description of studies

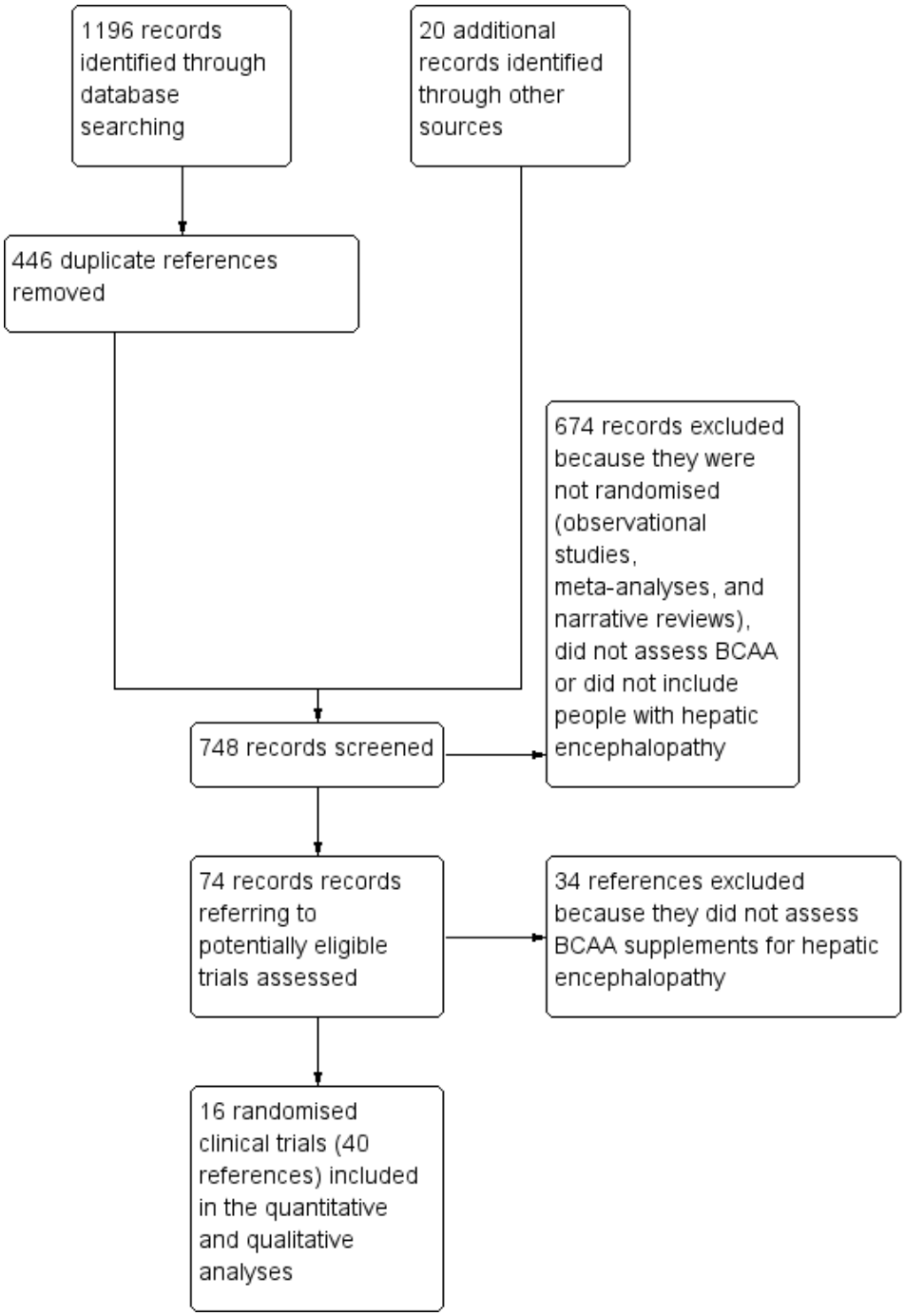
See: Characteristics of included studies; Characteristics of excluded studies.

We include 16 randomised clinical trials in the qualitative and quantitative analyses (Fiaccadori 1984; Horst 1984; Calvey 1985; Cerra 1985; Egberts 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Marchesini 1990; Vilstrup 1990; Hayashi 1991; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011). The trials included 827 participants with hepatic encephalopathy (97% had cirrhosis). The type of hepatic encephalopathy was minimal in four trials (Egberts 1985; Plauth 1993; Marchesini 2003; Les 2011), and overt in the remaining 12 trials. Eight trials assessed oral BCAA for minimal or overt hepatic encephalopathy (Horst 1984; Egberts 1985; Marchesini 1990; Hayashi 1991; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011). Seven trials assessed intravenous BCAA for overt hepatic encephalopathy (Fiaccadori 1984; Cerra 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Vilstrup 1990). One trial assessed oral or intravenous BCAA versus a control diet for overt hepatic encephalopathy (Cerra 1985). In the eight trials studying oral BCAA, people in the control group received placebo/no intervention or diets. In the seven trials studying intravenous BCAA, people in the control groups received placebo/no intervention or diets (Michel 1985; Hwang 1988; Vilstrup 1990), neomycin (Cerra 1985; Strauss 1986), or lactulose (Fiaccadori 1984; Rossi-Fanelli 1986).

Results of the search

We identified 1196 potentially relevant records in the electronic searches and 20 additional records in the manual searches (Figure 1). Of these, 40 records that referred to 16 randomised clinical trials fulfilled our inclusion criteria. We found one trial published in abstract form (Hayashi 1991), and 15 trials described in full paper articles (Fiaccadori 1984; Horst 1984; Calvey 1985; Cerra 1985; Egberts 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Marchesini 1990; Vilstrup 1990; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011). We were able to obtain unpublished information about the trial design (Characteristics of included studies) and data that allowed re-calculation of outcomes based on the individual participant data for four trials (Marchesini 1990; Marchesini 2003; Muto 2005; Les 2011). Four authors of the present review (IL, JC, GM, and HV) were investigators on included randomised clinical trials (Marchesini 1990; Vilstrup 1990; Marchesini 2003; Les 2011).

Figure 1. Study flow diagram. BCAA: branched-chain amino acids.



Included studies

Participants

The trials included 827 participants with hepatic encephalopathy. None used BCAA deficiency in their inclusion or exclusion criteria. Most participants (97%) had cirrhosis. The proportion of men ranged from 47% to 90%, the proportion of people with alcoholic liver disease ranged from 8% to 100%, and the proportion of people with viral hepatitis ranged from 0% to 81%. The mean age ranged from 47 to 64 years. In four trials, 6% to 74% of people had hepatic encephalopathy at baseline (we only included data on the people with hepatic encephalopathy in our analyses) (Horst 1984; Marchesini 2003; Muto 2005; Les 2011). The type of hepatic encephalopathy was minimal in four trials (Egberts 1985; Plauth 1993; Marchesini 2003; Les 2011), and overt in the remaining 11 trials (Fiaccadori 1984; Horst 1984; Calvey 1985; Cerra 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Marchesini 1990; Vilstrup 1990; Muto 2005).

Interventions

In one trial, most participants received oral BCAA and people who deteriorated received intravenous BCAA (Calvey 1985). Seven trials assessed oral BCAA (Horst 1984; Egberts 1985; Marchesini 1990; Hayashi 1991; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011), or intravenous BCAA (Fiaccadori 1984; Cerra 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Vilstrup 1990). Trials studying intravenous BCAA treated people in hospital and the remainder on an outpatient basis. The dose of BCAA ranged from 11 g/day to 57 g/day (median 20 g/day) and treatment duration from one to 104 weeks (median four weeks).

Comparisons

The control groups received placebo/no intervention in two trials (Hwang 1988; Plauth 1993). The type of BCAA in these two trials was oral (Plauth 1993), or intravenous (Hwang 1988). In 10 trials, participants were allocated to BCAA versus diets (Horst 1984; Calvey 1985; Egberts 1985; Michel 1985; Marchesini 1990; Vilstrup 1990; Hayashi 1991; Marchesini 2003; Muto 2005; Les 2011). The experimental intervention in these trials was oral BCAA (Horst 1984; Calvey 1985; Egberts 1985; Marchesini 1990; Hayashi 1991; Marchesini 2003; Muto 2005; Les 2011), or intravenous BCAA (Michel 1985; Vilstrup 1990). Four trials compared intravenous BCAA versus lactulose (Fiaccadori 1984; Rossi-Fanelli 1986), or neomycin (Cerra 1985; Strauss 1986).

Outcomes

One trial did not report mortality (Hayashi 1991). The remaining trials reported mortality at the end of treatment. All trials reported the effect of BCAA on hepatic encephalopathy. Twelve trials assessed the effect of BCAA on manifestations of overt hepatic encephalopathy (Fiaccadori 1984; Horst 1984; Calvey 1985; Cerra 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Marchesini 1990; Vilstrup 1990; Hayashi 1991; Muto 2005), and four trials of minimal hepatic encephalopathy (Egberts 1985; Plauth 1993; Marchesini 2003; Les 2011).

Excluded studies

The excluded trials were quasi-randomised studies in which different BCAA regimens were compared, or people without hepatic encephalopathy were assessed (Characteristics of excluded studies). We were unable to gather data on adverse events from these studies. We did not identify any ongoing trials.

Risk of bias in included studies

The assessment of bias (Figure 2; Figure 3) included information retrieved from the published trial reports as well as information obtained from the primary investigators (Characteristics of included studies).

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study. CHBG: Cochrane Hepato-Biliary Group.

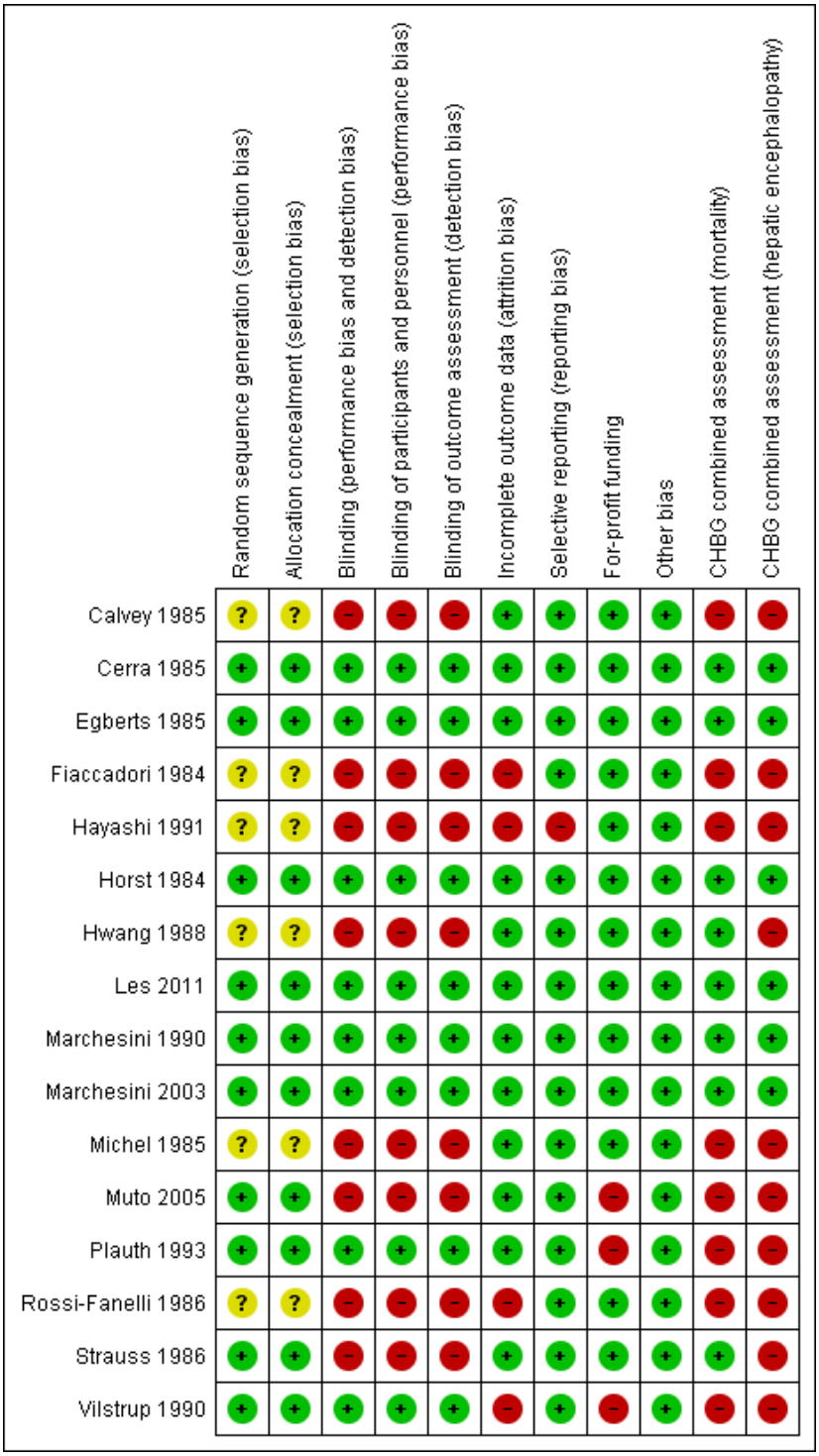
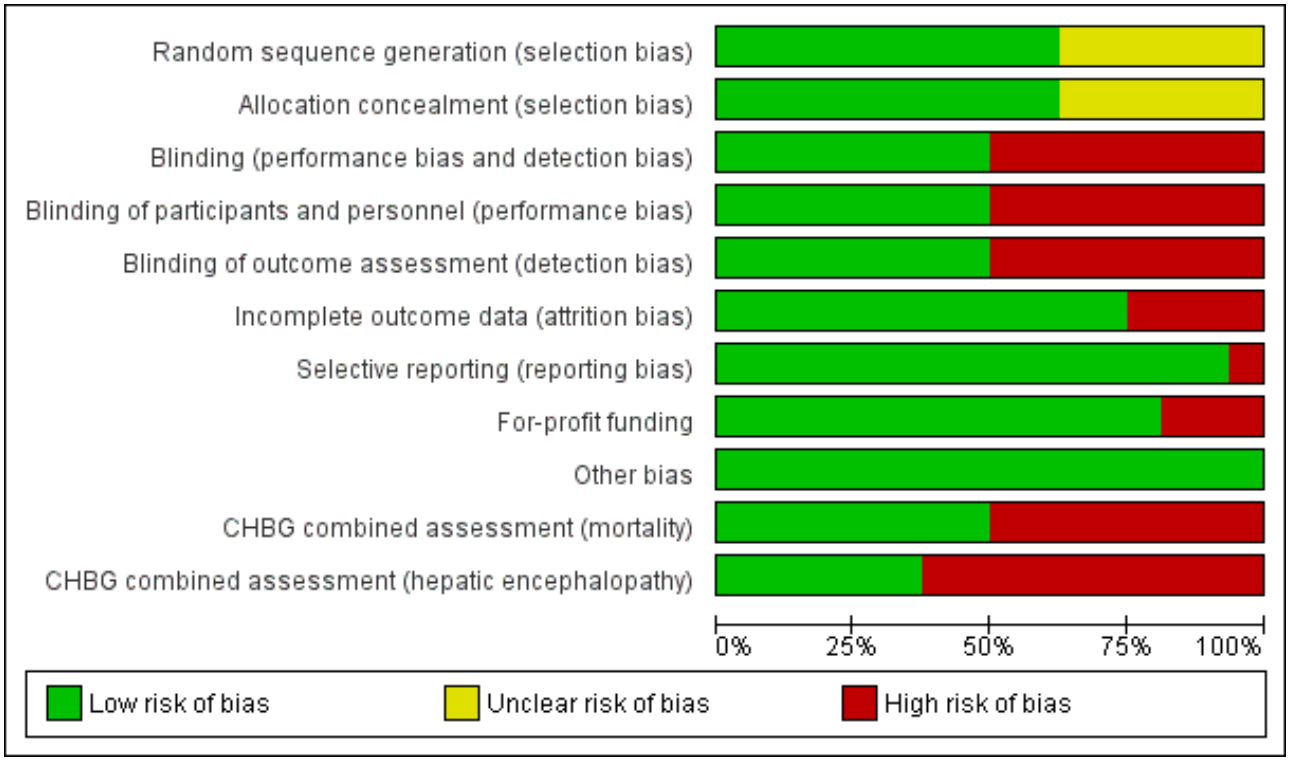


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. CHBG: Cochrane Hepato-Biliary Group.



Allocation

Sequence generation and allocation concealment

Based on the information that we collected from the published reports and information from authors, we classed the allocation sequence generation and allocation concealment as low risk of bias in 10 trials (Horst 1984; Cerra 1985; Egberts 1985; Strauss 1986; Marchesini 1990; Vilstrup 1990; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011). We classed the sequence generation and/or allocation concealment as unclear in the remaining six trials (Fiaccadori 1984; Calvey 1985; Michel 1985; Rossi-Fanelli 1986; Hwang 1988; Hayashi 1991).

Blinding

Seven trials were open without blinding of participants or investigators (Fiaccadori 1984; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Hayashi 1991; Muto 2005). We classed these trials as having a high risk of bias in the assessment of hepatic encephalopathy, adverse events, and quality of life. Nine trials were double blind with blinding of participants and personnel, and blinded outcome assessment. We classed them as low risk of performance and detection bias (Horst 1984; Calvey 1985; Cerra 1985; Egberts 1985; Marchesini 1990; Vilstrup 1990; Plauth 1993; Marchesini 2003; Les 2011).

Incomplete outcome data

We classed four trials as having a high risk of attrition bias because they did not account for participants with missing outcomes (Fiaccadori 1984; Rossi-Fanelli 1986; Vilstrup 1990; Hayashi 1991), and the remaining 12 trials as low risk of attrition bias (Horst 1984; Calvey 1985; Cerra 1985; Egberts 1985; Michel 1985; Strauss 1986; Hwang 1988; Marchesini 1990; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011).

Selective reporting

One trial published in abstract form did not report mortality (Hayashi 1991). We classed the trial as having a high risk of reporting bias. We had access to protocols for four trials (Marchesini 1990; Vilstrup 1990; Marchesini 2003; Les 2011). All four trials reported pre-defined outcomes including mortality and hepatic encephalopathy. We found that 15 trials reported the pre-defined outcomes (mortality and hepatic encephalopathy). We classed these 15 trials as having a low risk of reporting bias (Fiaccadori 1984; Horst 1984; Calvey 1985; Cerra 1985; Egberts 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Marchesini 1990; Vilstrup 1990; Plauth 1993; Marchesini 2003; Muto 2005; Les 2011).

For-profit funding

Three trials received support from for-profit organisations in the form of interventions (Plauth 1993; Vilstrup 1990; Muto 2005). We classed these trials as high risk of bias for this domain. None of the remaining 14 trials received support from for-profit organisations (Fiaccadori 1984; Horst 1984; Calvey 1985; Cerra 1985; Egberts 1985; Michel 1985; Rossi-Fanelli 1986; Strauss 1986; Hwang 1988; Marchesini 1990; Vilstrup 1990; Hayashi 1991; Marchesini 2003; Muto 2005; Les 2011).

Other potential sources of bias

We did not identify other biases for any of the included trials.

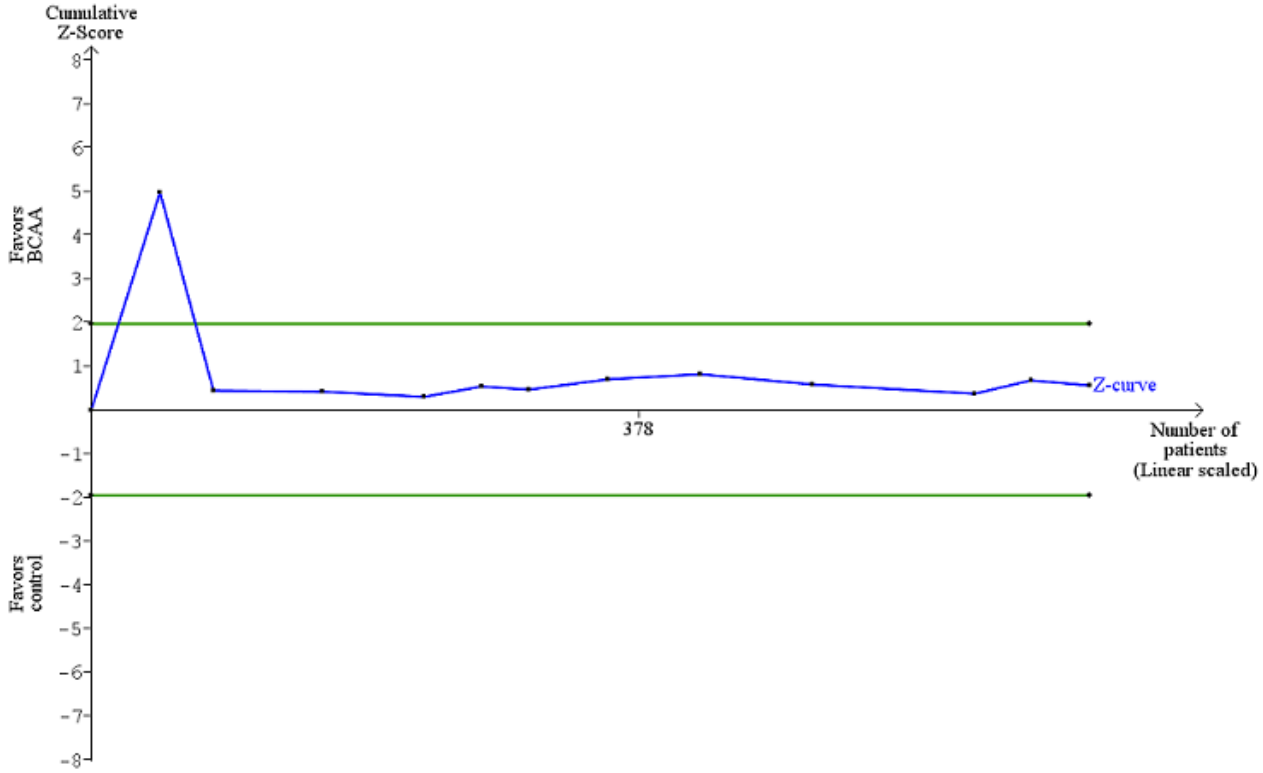
Effects of interventions

See: **Summary of findings for the main comparison** Branched-chain amino acids (BCAA) versus control for hepatic encephalopathy

Mortality

In total, 78 of 367 participants in the BCAA group versus 89 of 393 participants in the control group died (Analysis 1.1). Random-effects meta-analysis showed no difference between the groups (RR 0.88, 95% CI 0.69 to 1.11; 760 participants; 15 trials). The between-trial heterogeneity was unimportant (I^2 = 9%). The trial sequential analysis ignored the monitoring boundaries because the information in the cumulative meta-analysis was insufficient (Figure 4). Accordingly, the analysis suggested that we do not have firm evidence to support or refute the effect of BCAA on mortality. Subgroup analyses of mortality found no difference between oral or intravenous BCAA (RR 0.90, 95% CI 0.50 to 1.63 for oral; RR 0.90, 95% CI 0.63 to 1.28; for intravenous; Analysis 1.2), overt or minimal hepatic encephalopathy (Analysis 1.3), different types of control interventions (Analysis 1.4), or the type of data (Analysis 1.5). We did not perform a subgroup analysis to determine the effect of publication status because only trials published as full-paper articles reported mortality. The random-effects meta-regression found no predictors of heterogeneity for mortality (duration of therapy: P value = 0.37; dose of BCAA: P value = 0.57). In sensitivity analyses limited to trials with a low risk of bias, there was no effect of BCAA on mortality (Analysis 1.6). Mortality did not differ between the intervention groups in simple imputation with all losses to follow-up counted as treatment failures (RR 0.95, 95% CI 0.81 to 1.12) or in a worst-case scenario analysis with participants randomised to BCAA counted as treatment failures and controls as treatment successes (RR 0.96, 95% CI 0.76 to 1.20). There were no small-study effects (P value = 0.40). None of the participants died in the trial that included people with or without cirrhosis (Calvey 1985), so exclusion of the trial had no influence on the overall result.

Figure 4. Trial sequential analysis of branched-chain amino acids (BCAA) versus control interventions (placebo, no intervention, neomycin, or lactulose) for mortality in people with hepatic encephalopathy. The blue line (Z-curve) shows the cumulative meta-analysis adding the results of individual trials based on the year of publication. The vertical green line represents the 5% level of significance. The monitoring boundary (and futility) was ignored because the number of events and participants included in the analysis was insufficient. In the sequential analysis, we set alpha to 5%, power to 80%, control group incidence to 25%, relative risk reduction to 5%, and heterogeneity correction to 17%. The estimated information size was 23,485 participants. In total, the number of participants randomised was 367 in the BCAA group and 393 in the control groups.

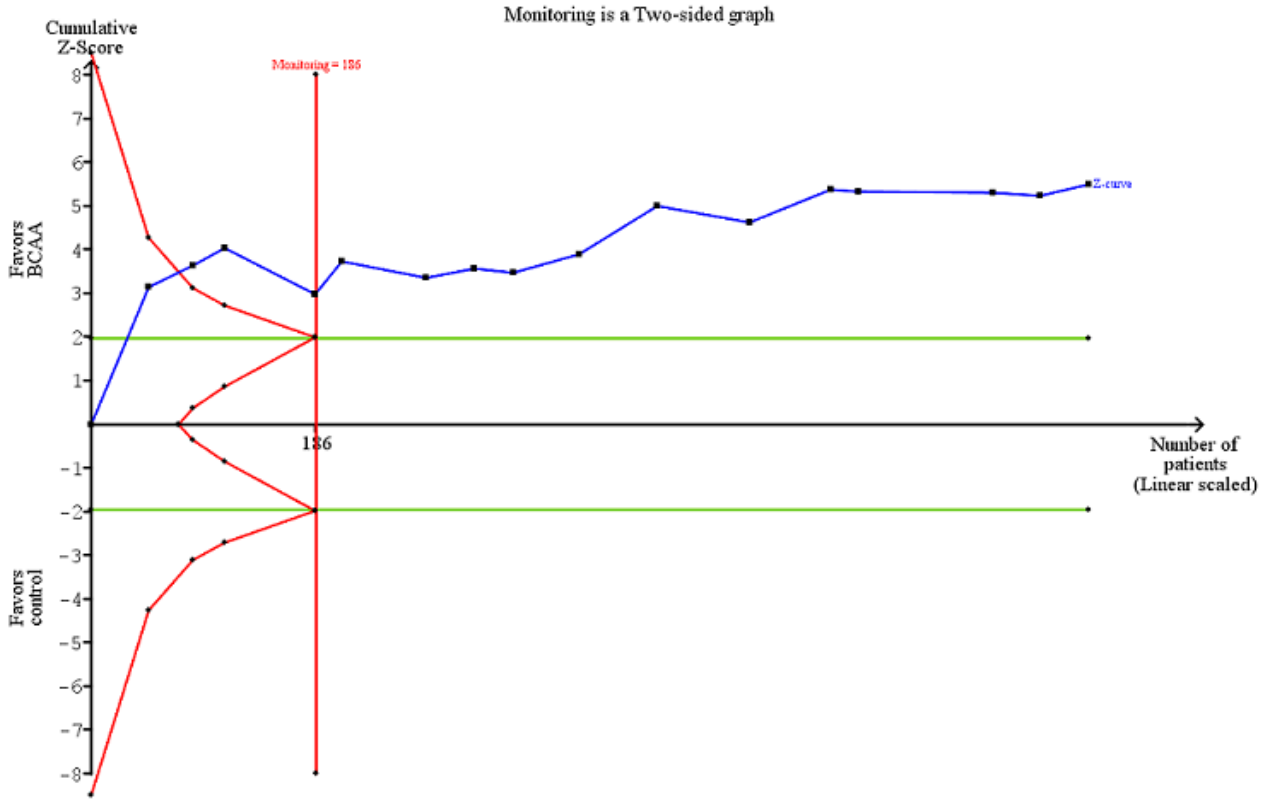


Hepatic encephalopathy

We gathered data on hepatic encephalopathy from all trials (Analysis 1.7). Random-effects meta-analysis showed that BCAA was associated with a beneficial effect on hepatic encephalopathy compared with controls (RR 0.73, 95% CI 0.61 to 0.88; 827 participants). The between-trial heterogeneity was moderate (I^2 =

51%). In trial sequential analysis (Figure 5), the cumulative Z-curve crossed the monitoring boundary before the required information size (also known as the diversity-adjusted required information size), which was 186 participants. When we repeated the analysis with a lower control group event rate and a lower RRR (adjusted for the potential risk of bias), the Z-curve crossed the monitoring boundary after inclusion of 546 participants before the required information size, which was 557 participants. Subgroup analysis found an effect of oral, but not intravenous BCAA (oral: RR 0.67, 95% CI 0.52 to 0.88; 430 participants; intravenous: RR 0.81, 95% CI 0.61 to 1.08; 397 participants; test for subgroup differences P value = 0.34; Analysis 1.8). There were no differences between trials stratified in subgroups based on the type of hepatic encephalopathy (P value = 0.83; Analysis 1.9), control groups (P value = 0.26; Analysis 1.10), published or re-calculated data (P value = 0.47; Analysis 1.11), or publication status (P value = 0.47; Analysis 1.12). In sensitivity analyses, BCAA had a beneficial effect on hepatic encephalopathy in trials with a low risk of bias (Analysis 1.13). There were no small-study effects (P value = 0.22). The benefit of BCAA on hepatic encephalopathy was confirmed in an analysis that counted all participants with missing outcomes as treatment failures (RR 1.32, 95% CI 1.15 to 1.51) and in a worst-case scenario analysis that counted participants randomised to BCAA as treatment failures and controls as treatment successes (RR 1.19, 95% CI 1.08 to 1.31). In one post-hoc analysis that excluded the trial on people with acute liver disease with or without cirrhosis (Calvey 1985), BCAA had a beneficial effect on hepatic encephalopathy (RR 0.74, 95% CI 0.62 to 0.89; Analysis 1.14). BCAA was also associated with a beneficial effect on mortality when excluding trials with a lactulose or neomycin control group (RR 0.76, 95% CI 0.63 to 0.92; 610 participants; 11 trials; I^2 = 52%; Analysis 1.15), but not when the analysis only included trials with a lactulose or neomycin control (RR 0.66, 95% CI 0.34 to 1.30; 195 participants; 4 trials; I^2 = 46%; Analysis 1.16).

Figure 5. Trial sequential analysis of branched-chain amino acids (BCAA) versus control interventions (placebo, no intervention, neomycin, or lactulose) for hepatic encephalopathy. The blue line (Z-curve) shows the cumulative meta-analysis adding the results of individual trials based on the year of publication. The vertical line represents the 5% level of significance. The monitoring boundary (inward sloping red line) shows the significance level after adjusting for the cumulative analysis. The horizontal green line shows the required information size (the number of participants needed to determine if firm evidence was established). We conducted the trial sequential analysis with alpha set to 5%, power to 80%, control group event rate to 63%, relative risk reduction to 45%, and heterogeneity correction to 47%. The estimated required information size was 186 participants (diversity adjusted). In total, the cumulative meta-analysis included 402 participants in the BCAA group and 425 in the control groups.



In univariable meta-regression analyses, we found no effect of the dose of BCAA (P value = 0.09), duration of treatment (P value = 0.21), or mode of administration (P value = 0.35). When combining the three potential predictors, multi-level meta-regression analysis showed no effect of the dose (P value = 0.50), mode of administration (P value = 0.82), or treatment

duration (P value = 0.57). In univariable meta-regression analyses on participant characteristics, we reached a similar conclusion for the type of hepatic encephalopathy (P value = 0.07), mean age of included participants (P value = 0.50), proportion of men (P value = 0.94), proportion of people with alcoholic liver disease (P value = 0.09), and proportion of people with viral hepatitis (P value = 0.94). Likewise, we found no effect of the type of control group when analysed combined (placebo/no intervention, diet, lactulose, neomycin; P value = 0.75) or in separate assessments of placebo/no intervention (P value = 0.75), any diet (P value = 0.20), isonitrogenous isocaloric diet (P value = 0.80), neomycin (P value = 0.24), or lactulose (P value = 0.11). In multi-level meta-regression analyses with backwards elimination of all potential predictors, none remained in the model.

Adverse events

The trials did not report serious adverse events (apart from mortality). The most common non-serious adverse event was gastrointestinal discomfort (non-specific gastrointestinal symptoms that included both nausea and diarrhoea), which occurred in about 50 of 442 (11%) participants in the BCAA group and 11 of 503 (2%) participants randomised to control diets (Analysis 1.17). BCAA increased the risk of nausea and diarrhoea in fixed-effect meta-analysis (RR 5.56, 95% CI 2.93 to 10.55), but not in random-effects meta-analysis (RR 3.39, 95% CI 0.70 to 16.46).

Quality of life

Three trials studying oral BCAA supplements evaluated the quality of life scores at baseline and end of treatment based on the 36-item Short Form (SF-36) questionnaire (Marchesini 2003; Muto 2005; Les 2011). Due to the methods used to register scores, we were unable to combine the results in meta-analyses. All trials included people with cirrhosis. Some of the included participants did not have hepatic encephalopathy at baseline. When the analyses were limited to people with hepatic encephalopathy, none of the trials found beneficial or harmful effect of BCAA on the global SF-36 score or any of the subscales.

Nutritional outcomes

The included trials did not perform comparable assessments of nutritional parameters. A meta-analysis of three trials with diet controls showed no difference in post-treatment albumin between the BCAA and control groups (MD 0.60, 95% CI -0.90 to 2.09; Analysis 1.18). Analysis of one trial with a neomycin control group and two trials with isonitrogenous controls showed no difference between intervention groups regarding nitrogen balance (SMD 0.81, 95% CI 0.07 to 1.56; Analysis 1.19).

Summary of findings

We have presented the key results on the outcomes mortality, hepatic encephalopathy, adverse events, and nutritional outcomes, and grading of the quality of the evidence in Summary of findings for the main comparison. We showed the result of the primary meta-analysis for each outcome measure. As shown in the table, we only graded the quality of the evidence as 'high' for the outcome hepatic encephalopathy. We downgraded the evidence quality to 'moderate' for the remaining outcome measures, mainly due to imprecision.

DISCUSSION

Summary of main results

This review included 16 randomised clinical trials published from 1984 to 2011. Nearly all included participants had cirrhosis (97%). The trials compared BCAA versus placebo/no intervention, diets, lactulose, or neomycin. The results showed that BCAA have a beneficial effect on manifestations of hepatic encephalopathy. The between-trial heterogeneity was moderate, but none of the subgroup, sensitivity, or regression analyses was able to explain the heterogeneity. Different subgroup analyses showed a beneficial effect of oral, but not intravenous BCAA, and an effect of BCAA in trials on overt hepatic encephalopathy, but not on minimal hepatic encephalopathy. BCAA had a beneficial effect on hepatic encephalopathy when excluding trials with a lactulose or neomycin control group, but not in an analysis limited to trials with these two type of controls. However, the relatively small number of trials in the different subgroups limited the strength of the findings. Furthermore, none of the trials included several intervention arms comparing different types of BCAA or different control regimens. Additional analyses found that BCAA were associated with the gastrointestinal adverse events, diarrhoea and nausea, which occurred in about 1 in 10 people. We found no beneficial or detrimental effects of BCAA on the quality of life or nutritional outcomes.

Overall completeness and applicability of evidence

Recent guidelines recommend routine treatment of people with overt hepatic encephalopathy (AASLD and EASL guideline 2014a; AASLD and EASL guideline 2014b). Oral BCAA are recommended as an alternative or add-on therapy to the first-line treatment, which is non-absorbable disaccharides. Our findings support the use of BCAA in clinical practice, but do not provide enough evidence to evaluate the benefit of BCAA compared with other interventions.

The cost effectiveness of interventions for the management of people with hepatic encephalopathy is important. Economic studies show that the total charges related to hepatic encephalopathy in the United States increased from $USD 4676.7 million in 2005 to $USD 7244.7 million in 2009 (Stepanova 2012). We did not assess the costs associated with hepatic encephalopathy, but our data may be used in future pharmacoeconomic reviews.

The present systematic review (as well as the previous version) included a heterogeneous group of trials. We decided to keep the broad scope of the review to identify common features within similar interventions. Grouping increases the external validity and consistency of the findings making it possible to assess the intervention effect across a wider range of settings and patient populations. The strategy also reduces chance results that can occur when analysing several smaller subgroups (Weir 2012). In theory, grouping makes it possible to make better judgements about the consistency of observed effects across trials and to look for differences between interventions, settings, and participant characteristics. We did not identify predictors of between-trial heterogeneity. None of the intervention or participant characteristics explained heterogeneity. However, we did not have enough data to exclude the possibility that there may be specific patient populations who benefit more or less from BCAA.

The diagnostic criteria used in individual trials varied. The variation largely reflected the differences that were occurred between the publication of the first trials in 1984 to (Fiaccadori 1984; Horst 1984) to the publication of the latest trial in 2005 (Muto 2005). Using a systematic approach to the assessment of hepatic encephalopathy was essential (Bajaj 2011). The included trials used methods such as the West Haven Criteria that are used in clinical practice (Ferenci 2002; Mullen 2007; Bajaj 2008). This system grades symptoms from a clinically normal mental state (grade 0) over trivial signs such as shortened attention span to deep coma (grade 4). The clinically normal state includes people without overt hepatic encephalopathy and people with minimal hepatic encephalopathy that can be identified through psychometric testing such as the number connection test (Bajaj 2008; Bajaj 2011). In one cohort study of 217 people with cirrhosis, repeated evaluations showed that hepatic encephalopathy was not classed correctly in more than one third of people (Kircheis 2007). Therefore, thorough assessments are important. Likewise, careful evaluation is required to evaluate whether manifestations of hepatic encephalopathy is improved. Based on the differences in the diagnostic criteria, the assessment of this outcome measure varied in included trials. We chose to use the information and evaluation made by the original investigators. The extent to which manifestations improved will depend on the pre-defined criteria and the overall assessment is likely to involve some degree of subjective assessment. In spite of these limitations, the definition and assessment of outcomes reflect current clinical practice (Weissenborn 2013).

One study found that BCAA supplementation increased ammonia levels in people with cirrhosis and healthy participants (Dam 2011). BCAA have a stimulatory effect on ammonia detoxification to glutamine and decreased concentrations in liver cirrhosis (Holecek 2013). The reasons for the BCAA deficiency in cirrhosis include consumption in skeletal muscle for synthesis of glutamate. We were unable to determine the effect of BCAA in relation to the baseline BCAA concentrations or sarcopenia or ammonia levels. We found few data to determine the effect of BCAA on nutrition.

Quality of the evidence

When assessing the quality of the included trials, the internal as well as the external validity was important. Without adequate internal validity, the question of external validity becomes unimportant. Without adequate external validity, the trial may be clinically irrelevant in spite of an excellent basic methodology. In the assessment of internal validity, the control of bias associated with randomisation and blinding is important because it may lead to overestimated intervention effects (Wood 2008; Savovic 2012). When evaluating the effect of bias, we estimated that lack of blinding would not affect the assessment of mortality or laboratory parameters. In a study including 1973 randomised clinical trials from 234 meta-analyses (Savovic 2012), authors found trials with inadequate or unclear (compared with adequate) sequence generation or allocation concealment overestimated intervention effects. The degree of bias was greatest for subjective outcomes and there was little evidence of bias for all-cause mortality (relative odds ratio 0.89, credibility interval 0.75 to 1.05). Lack of, or unclear, double blinding (compared with double blinding) was associated with a mean 13% exaggeration of intervention effects. Again, bias was detected in analyses of subjective outcomes and not for all-cause mortality. When we included the trials with a low risk of bias, we found no effect of BCAA on mortality, but a beneficial effect on hepatic encephalopathy when analysing bias domains separately or combined.

Some trials on BCAA used a cross-over design (Egberts 1985; Plauth 1993).The benefit of the design includes comparable control groups and increased statistical power. The use of the design in hepatic encephalopathy is debatable because the condition is a naturally fluctuating disease and because people may die during the first treatment period. Therefore, we chose to use only the first period of the cross-over trials in spite of the potential loss of information that this strategy entails (Lathyris 2007). The duration of therapy ranged from one to 104 weeks. Because we used the first treatment period from cross-over trials, the information that we included from the cross-over trials was based on a relatively shorter follow-up than trials using a parallel arm design. In our subgroup analyses, we found no difference between cross-over and parallel arm trials, and the duration of follow-up did not predict the treatment effect in our meta-regression. However, we cannot exclude the possibility that the duration of follow-up and trial design may be important.

Potential biases in the review process

The main potential bias in the review process is that we only had access to the published data from some of the included trials. We found no difference between the subgroups of trials with published summary data and trials for which we re-calculated outcomes for people with hepatic encephalopathy at baseline. On the one hand, this supports the strength of our findings. On the other hand, we cannot exclude that we would have been able to retrieve additional information if we had access to unpublished as well as published data from all trials. Two of the included trials were only published in abstract form (Fiaccadori 1984; Hayashi 1991). In some trials, the complete results presented in the final full-text article differed from the initial analyses presented in abstract form (Gluud 2010). Access to the original patient data from trials published in abstract form may increase the strength of the analyses. Due to the risk of publication bias, we did not exclude unpublished trials and trials published in abstract form to avoid overestimation of intervention benefits.

Agreements and disagreements with other studies or reviews

The previous version of this review included 11 randomised clinical trials with 556 participants (Als-Nielsen 2003). This updated review included 16 trials with 827 participants. Both versions of the review included trials on oral or intravenous BCAA versus any control intervention. In both reviews, BCAA was not associated with reduced mortality. Likewise, both reviews found that BCAA was associated with a beneficial effect on hepatic encephalopathy. The previous review found that BCAA had a beneficial effect on improved manifestations of hepatic encephalopathy with an RR of 1.31 and an I^2 of 51%. The analysis included nine trials with a placebo/no intervention, diet, lactulose, or neomycin control group. In an analysis that included the same control groups, we included 16 trials and found that BCAA was associated with a beneficial effect on hepatic encephalopathy assessed based on the number of participants without improved manifestations with a RR of 0.73 and an I^2 of 51%. The previous review concluded that the evidence was not convincing mainly because the subgroup analyses found no effect of BCAA on hepatic encephalopathy when analysing each domain separately. In the present review, an analysis that was limited to trials with a low risk of bias confirmed

that BCAA has a beneficial effect on hepatic encephalopathy. Accordingly, the overall quantitative result of the two reviews concur, but only the updated review provided enough evidence from trials with an adequate control of bias.

One comprehensive Cochrane review from 2012 included randomised clinical trials on any type of nutritional support for any type of liver disease (Koretz 2012). The review found no difference in mortality between nutritional therapy versus no nutritional therapy for liver disease in a medical setting. One meta-analysis of six trials (total 119 participants) found that nutritional supplements had a beneficial effect on resolution of hepatic encephalopathy. Two of the six trials evaluated BCAA (Calvey 1985; Hayashi 1991). One of the trials included people with acute alcoholic hepatitis (Calvey 1985). The trial found no differences between BCAA and control groups regarding mortality, hepatic encephalopathy, or nutritional parameters. The second trial included people with cirrhosis and found a beneficial effect of BCAA on improvement of hepatic encephalopathy (Hayashi 1991). The systematic review found that the effect of nutritional supplements on hepatic encephalopathy was more pronounced in subgroup analyses of trials with a high concentration of BCAA (Koretz 2012). However, there was unclear control of bias and the total number of participants was small. Still the overall result concurred with our findings.

AUTHORS' CONCLUSIONS

Implications for practice

This review found that branched-chain amino acid (BCAA) was associated with a beneficial effect on hepatic encephalopathy associated with cirrhosis. The evidence suggested that BCAA should be considered in the management of people with hepatic encephalopathy. Adverse events were non-serious and mainly included gastrointestinal symptoms. There was no evidence to support or refute an effect of BCAA on mortality, quality of life, or nutritional outcomes.

Implications for research

We need additional high-quality trials to evaluate the effect of BCAA combined with interventions that are used in clinical practice such as antibiotics and lactulose (AASLD and EASL guideline 2014a; AASLD and EASL guideline 2014b). We also need trials on people with minimal hepatic encephalopathy and trials with data on the quality of life and nutritional parameters. Additional research is also needed to evaluate if BCAA has a beneficial effect on hepatic encephalopathy in people with acute liver failure without cirrhosis and to identify if specific subgroups of people benefit from treatment with BCAA.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Calvey 1985

Methods	Parallel arm randomised clinical trial comparing BCAA versus non-isonitrogenous diet.
Participants	26 people with overt hepatic encephalopathy. • Proportion with cirrhosis 47%. • Proportion with alcoholic liver disease 100%. • Proportion with viral hepatitis 0%. • Proportion of men 48%.

Calvey 1985 *(Continued)*

	• Median age BCAA group 49 years. • Median age control groups 49 years.
Interventions	BCAA 20 g/day versus standard diet or standard diet plus conventional protein supplements for 3 weeks (2 control groups).
Outcomes	• Hepatic encephalopathy was graded clinically using a modified 0- to 5-point Glasgow Coma Score and the Reitan Trail-Making Test. • Mortality and hepatic encephalopathy assessed after 3 weeks.
Country of origin	UK.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Oral or intravenous (people who deteriorated).
Notes	• The trial included 64 people with acute alcoholic hepatitis. Only people with overt hepatic encephalopathy at baseline were included in our analyses. • The inclusion period was August 1980 to March 1983. • The trial included 3 intervention arms. We combined data from the 2 control arms in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding reported.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes are defined and reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.

Calvey 1985 *(Continued)*

CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Cerra 1985

Methods	Parallel arm randomised clinical trial comparing BCAA versus neomycin.
Participants	75 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 100%. • Proportion with viral hepatitis 0%. • Proportion of men 86%. • Mean age BCAA group 53 years. • Mean age control group 53 years.
Interventions	BCAA (36% BCAA solution 1.5 to 3 L/day) versus neomycin (4 g/day) for 4 days.
Outcomes	• Hepatic encephalopathy was assessed using a 0- to 4-point score. • Mortality and hepatic encephalopathy assessed after 4 days.
Country of origin	USA.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	• The investigators crossed participants classed as non-responders over after 4 days. Data received on the number of people with clinical outcomes after the first 4 days of treatment received and included in our analyses (used in the previous version of this review). • The investigators classed participants as having acute hepatic encephalopathy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy trial.
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded.

Cerra 1985 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were defined and reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	Low risk	Low risk of bias when domains were combined.

Egberts 1985

Methods	Cross-over randomised clinical trial comparing BCAA versus isonitrogenous diet.
Participants	22 people with minimal hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 86%. • Proportion with viral hepatitis 14%. • Proportion of men 73%. • Mean age BCAA group 51 years. • Mean age control group 52 years.
Interventions	Oral BCAA (0.25 g/kg/day) versus isonitrogenous diet for 7 days.
Outcomes	• Hepatic encephalopathy was assessed the following scales: Culture Fair Intelligence Test, Wechsler Adult Intelligence Test, Digit Symbols, Multiple Choice Vocabulary Test, Visual Retention Test, Number Revision Test, Attention Stress Test, Attention Diagnostic Method, Motor Performance Test Battery, and Vienna Reaction Time Apparatus. • Mortality and hepatic encephalopathy assessed after 7 days.
Country of origin	Germany.
Type of hepatic encephalopathy	Minimal.
BCAA mode of administration	Oral.
Notes	• Only data from the first treatment period were included in the analyses of mortality and hepatic encephalopathy. Additional information received on the study design.

Egberts 1985 *(Continued)*

- Trial inclusion period was June 1983 to June 1986.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (table of random numbers).
Allocation concealment (selection bias)	Low risk	Identically appearing drug containers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, placebo controlled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures defined and reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	Low risk	Low risk of bias when domains were combined.

Fiaccadori 1984

Methods	Parallel arm randomised clinical trial comparing BCAA alone or with lactulose versus lactulose alone.
Participants	48 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 52%. • Proportion with viral hepatitis 32%. • Proportion of men 73%. • Mean age in BCAA group 51 years. • Mean age control group 51 years.

Fiaccadori 1984 *(Continued)*

Interventions	BCAA (2 L/day) alone or with lactulose versus lactulose 150-300 mL/day for 7 days.
Outcomes	Hepatic encephalopathy was graded based on clinical evaluations, asterixis, blood ammonia, electroencephalography, and Reitan Number Connection Test.
Country of origin	Italy.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	• Abstract. • The investigators provided additional data on the design and number of participants with clinical outcomes (unpublished information/data also used in the previous version of this review). • The investigators classed participants as having acute hepatic encephalopathy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants excluded or lost to follow-up after randomisation were not described in the published report.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes not described in the published report (abstract). Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.

Fiaccadori 1984 *(Continued)*

CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Hayashi 1991

Methods	Parallel arm randomised clinical trial comparing BCAA versus isonitrogenous diet.
Participants	77 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 58%. • Proportion with viral hepatitis 9%. • Proportion of men 68%. • Mean age BCAA group and control group not reported.
Interventions	BCAA (11 g/day) versus isonitrogenous diet for 3 weeks.
Outcomes	• Clinical hepatic encephalopathy was assessed using a 4-point score, the Number Connection Test and Serial Seven Test. • Hepatic encephalopathy reported after 3 weeks. Mortality not reported.
Country of origin	Japan.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Oral.
Notes	• Abstract. • The investigators classed the type of hepatic encephalopathy as chronic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial without blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias)	High risk	Outcome assessment not blinded.

Hayashi 1991 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants with missing outcomes were not accounted for.
Selective reporting (reporting bias)	High risk	Mortality was not reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Horst 1984

Methods	Parallel arm randomised clinical trial comparing BCAA versus isonitrogenous diet.
Participants	37 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 38%. • Proportion with viral hepatitis 8%. • Proportion of men 65%. • Mean age BCAA group 57 years. • Mean age control group 60 years.
Interventions	BCAA 20 g/day increased to 80 g/day versus isonitrogenous placebo for 4 weeks.
Outcomes	• Hepatic encephalopathy graded using a 4-point score, the Number Connection Test, and electroencephalography. • Mortality and hepatic encephalopathy assessed after 4 weeks.
Country of origin	USA.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Oral.
Notes	The primary investigators classed participants as having chronic intermittent hepatic encephalopathy and sensitivity to dietary protein.

Risk of bias

Bias	Authors' judgement	Support for judgement

Horst 1984 *(Continued)*

Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	Numbered identical coded drug containers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, placebo controlled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures were defined and reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	Low risk	Low risk of bias when domains were combined.

Hwang 1988

Methods	Parallel arm randomised clinical trial comparing BCAA versus no intervention.
Participants	55 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 15%. • Proportion with viral hepatitis 65%. • Proportion of men 90%. • Mean age BCAA group 60 years. • Mean age control group 62 years.
Interventions	• Intravenous BCAA 40 g/day versus no intervention for 5 days.
Outcomes	• Hepatic encephalopathy graded using a 0- to 4-point scale. • Mortality and hepatic encephalopathy assessed after 5 days.

Hwang 1988 *(Continued)*

Country of origin	China.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	The investigators included 60 episodes of acute hepatic encephalopathy (in 55 participants). We only included each person once in our analyses and used data from the first time the person was randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial without blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were accounted for. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	High risk of bias when domains (excluding blinding) were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Les 2011

Methods	Parallel arm randomised clinical trial comparing BCAA versus isocaloric diet.
Participants	40 people with minimal hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 36%. • Proportion with viral hepatitis 53%. • Proportion of men 76%. • Mean age BCAA group 64 years. • Mean age control group 63 years.
Interventions	Enteral BCAA 29 g/day versus isocaloric placebo for 56 weeks.
Outcomes	• Hepatic encephalopathy was assessed using a 4-point score, Trail Making Test part A, Symbol Digit Test (oral version), and Grooved Pegboard Test (dominant hand). • Mortality and hepatic encephalopathy assessed after 56 weeks.
Country of origin	Spain.
Type of hepatic encephalopathy	Minimal.
BCAA mode of administration	Oral.
Notes	• Trial included people with previous episodes of hepatic encephalopathy. We re-calculated clinical outcomes for people with minimal hepatic encephalopathy at baseline. • 2 of the authors of this review (IL and JC) were investigators in the trial with access to the data and protocol. • Trial inclusion period was January 2003 to December 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation via identically appearing coded drug containers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, placebo controlled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	All participants accounted.

Les 2011 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures defined and reported. All outcomes were described as specified in the trial protocol.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	Low risk	Low risk of bias when domains were combined.

Marchesini 1990

Methods	Parallel arm randomised clinical trial comparing BCAA versus isonitrogenous control versus isocaloric casein-based control.
Participants	64 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 56%. • Proportion with viral hepatitis 41%. • Proportion of men 80%. • Mean age BCAA group 60 years. • Mean age both control groups 60 years.
Interventions	BCAA 2.4 g/10 kg/day versus isonitrogenous diet versus and isocaloric diet for 3 months.
Outcomes	• Hepatic encephalopathy was assessed using a 12-point score. • Mortality and hepatic encephalopathy assessed after 3 months.
Country of origin	Italy.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Oral.
Notes	• The trial included 2 control groups. • 1 of the authors of this review (GM) was an investigator in the trial with access to the participant data and trial protocol. In our analyses of the data, we combined the 2 control groups. • Trial inclusion period was January 1985 to December 1986.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number sequence.

Marchesini 1990 *(Continued)*

Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding, with blinded administration of active interventions and controls.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported. All outcomes were described as specified in the trial protocol.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	Low risk	Low risk of bias when domains were combined.

Marchesini 2003

Methods	Parallel arm randomised clinical trial comparing BCAA versus isonitrogenous and isocaloric casein-based control.
Participants	112 people with minimal hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 21%. • Proportion of men 63%. • Proportion with viral hepatitis 68%. • Mean age BCAA group 59 years. • Mean age control group 60 years.
Interventions	BCAA 7.2 g/day versus isonitrogenous versus isocaloric supplements for 12 months.
Outcomes	• Hepatic encephalopathy was assessed using a 4-point score and the Reitan Test. • Mortality and hepatic encephalopathy assessed after 12 months.
Country of origin	Italy.

Marchesini 2003 *(Continued)*

Type of hepatic encephalopathy	Minimal.
BCAA mode of administration	Oral.
Notes	• The trial included people with previous episodes of hepatic encephalopathy. • 1 of the authors of this review (GM) was an investigator in the trial with access to the patient data and trial protocol. We re-calculated clinical outcomes for people with minimal hepatic encephalopathy at baseline. • Trial inclusion period was March 1999 to March 2000.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding using identically appearing packets of BCAA and control supplements.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants with missing outcomes were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures were defined and reported. All outcomes were described as specified in the trial protocol.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	Low risk	Low risk of bias when domains were combined.

Michel 1985

Methods	Parallel arm randomised clinical trial comparing BCAA versus isonitrogenous and isocaloric control.
Participants	70 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 81%. • Proportion with viral hepatitis 11%. • Proportion of men 30%. • Mean age BCAA group 61 years. • Mean age control group 59 years.
Interventions	BCAA 6.25 to 12.5 g/day versus isonitrogenous and isocaloric control for 5 days.
Outcomes	• Hepatic encephalopathy assessed using 3-point scale. • Mortality and hepatic encephalopathy assessed after 5 and 36 days (1 month after treatment).
Country of origin	France.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	• We used the maximum duration of follow-up in our analyses (as specified in the methods section). • The investigators classed participants as having acute hepatic encephalopathy. • Trial inclusion period was January 1979 to January 1984.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clearly reported.
Allocation concealment (selection bias)	Unclear risk	Not clearly reported.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial without blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.

Michel 1985 *(Continued)*

Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Muto 2005

Methods	Parallel arm randomised clinical trial comparing BCAA versus non-isonitrogenous control diet.
Participants	39 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 8%. • Proportion with viral hepatitis 81%. • Proportion of men 47%. • Mean age BCAA group 62 years. • Mean age control group 61 years.
Interventions	BCAA 12 g/day versus standard diet for 2 years.
Outcomes	Hepatic encephalopathy was assessed using a 4-point scale.
Country of origin	Japan.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Oral.
Notes	• The trial included people with cirrhosis. A subgroup of people had hepatic encephalopathy (assessed as a grade of at least 1 using the West Haven Criteria). • We received data from the authors and the pharmaceutical company that funded the trial, which allowed re-calculation of clinical outcomes for people with hepatic encephalopathy at baseline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated (minimisation method).
Allocation concealment (selection bias)	Low risk	Central randomisation.

Muto 2005 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Open trial without blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes were defined and reported. Protocol not available.
For-profit funding	High risk	A pharmaceutical company producing BCAA funded the trial.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Plauth 1993

Methods	Cross-over randomised clinical trial comparing BCAA versus placebo.
Participants	23 people with minimal hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 88%. • Proportion with viral hepatitis 12%. • Proportion of men 65%. • Mean age BCAA group 52 years. • Mean age control group 49 years.
Interventions	BCAA 0.25 g/kg/day versus placebo for 8 weeks.
Outcomes	• Hepatic encephalopathy assessed using psychometric tests including the Digit Symbol and Number Connection Test, and test batteries on psychomotor function, attention, and reaction time. • Mortality and hepatic encephalopathy assessed after 8 weeks.
Country of origin	Germany.
Type of hepatic encephalopathy	Minimal.

Plauth 1993 *(Continued)*

BCAA mode of administration	Oral.
Notes	We only included data from the first treatment period in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated (block randomisation).
Allocation concealment (selection bias)	Low risk	Administration of coded drug containers.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding achieved using a placebo control.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants with missing outcomes were accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures defined and reported. Protocol not available.
For-profit funding	High risk	A pharmaceutical company supported the trial.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Rossi-Fanelli 1986

Methods	Parallel arm randomised clinical trial on BCAA versus lactulose.
Participants	40 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 32%. • Proportion with viral hepatitis 12%.

Rossi-Fanelli 1986 *(Continued)*

- Proportion of men 62%.
- Mean age BCAA group 59 years.
- Mean age control group 59 years.

Interventions	BCAA (57 g/day) versus lactulose (dose not reported) for 2 days.
Outcomes	• Hepatic encephalopathy assessed using a 4-point scale. • Mortality and hepatic encephalopathy assessed after 2 days.
Country of origin	Italy.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	• The investigators included people with acute hepatic encephalopathy and crossed participants classed as non-responders after 48 hours to the alternative treatment. Remaining participants continued on the allocated intervention. We included data from the first 48 hours in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial without blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment not blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants lost to follow-up or excluded after randomisation were not accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcomes defined and reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.

Rossi-Fanelli 1986 *(Continued)*

CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Strauss 1986

Methods	Parallel arm randomised clinical trial comparing BCAA versus neomycin.
Participants	32 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 75%. • Proportion with viral hepatitis 13%. • Proportion of men 90%. • Mean age BCAA group 51 years. • Mean age control group 54 years.
Interventions	BCAA (1.2 to 1.5 g/kg/day) versus neomycin (6 g/day) for a maximum of 5 days.
Outcomes	Hepatic encephalopathy assessed using a 4-point scale.
Country of origin	Brazil.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	The primary investigators provided additional information about clinical outcome measures (also used in the previous version of this review). The investigators included 3 participants twice. We only included the first randomisation period in our analyses (each participant was only included once in our analysis).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	Serially numbered opaque sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel not blinded.
Blinding of outcome assessment (detection bias)	High risk	Outcome assessment not blinded.

Strauss 1986 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for.
Selective reporting (reporting bias)	Low risk	Clinically relevant outcome measures were reported. Protocol not available.
For-profit funding	Low risk	No for-profit funding.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	Low risk	Low risk of bias when domains (except blinding) were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

Vilstrup 1990

Methods	Parallel arm randomised clinical trial comparing BCAA versus isonitrocaloric control.
Participants	77 people with overt hepatic encephalopathy. • Proportion with cirrhosis 100%. • Proportion with alcoholic liver disease 91%. • Proportion with viral hepatitis 9%. • Proportion of men 72%. • Mean age BCAA group 55 years. • Mean age control group 56 years.
Interventions	BCAA (12.5 mL/kg/day) versus isocaloric placebo for a maximum of 16 days.
Outcomes	• Hepatic encephalopathy assessed using a 4-point scale. • Mortality and hepatic encephalopathy assessed after 16 days.
Country of origin	Denmark.
Type of hepatic encephalopathy	Overt.
BCAA mode of administration	Intravenous.
Notes	• 1 of the authors of this review (HV) was an investigator in the trial with access to the protocol. The original trial data were no longer available, but all necessary data for our analyses of mortality and hepatic encephalopathy were included in the published trial.

Risk of bias

Bias	Authors' judgement	Support for judgement

Vilstrup 1990 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, placebo controlled.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants who completed the trial were included in the analyses.
Selective reporting (reporting bias)	Low risk	Primary outcome measures were specified and reported as specified in the trial protocol.
For-profit funding	High risk	A pharmaceutical company funded the interventions.
Other bias	Low risk	No other biases.
CHBG combined assessment (mortality)	High risk	High risk of bias when domains were combined.
CHBG combined assessment (hepatic encephalopathy)	High risk	High risk of bias when domains were combined.

BCAA: branched-chain amino acids; CHBG: Cochrane Hepato-Biliary Group.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Eriksson 1982	Quasi-randomised cross-over trial.
Hayashi 2007	Compared BCAA plus zinc versus BCAA alone.
Malaguarnera 2009	Randomised trial comparing BCAA plus L-acetylcarnitine versus BCAA alone.
O'Keefe 1987	Compared different BCAA supplements.
Wahren 1983	Quasi-randomised study.
Walker 1982	Compared different BCAA supplements.

BCAA: branched-chain amino acids.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12610001021066

Trial name or title	The Effects of Supplementation with Synbiotics, Branched Chain Amino Acids on Levels of Hepatic Encephalopathy in Patients with Cirrhosis.
Methods	Parallel arm randomised clinical trial.
Participants	Adults with Childs B or C cirrhosis on lactulose.
Interventions	BCAA plus synbiotics versus BCAAs plus placebo versus synbiotics plus placebo.
Outcomes	Levels of hepatic encephalopathy assessed using the Trail Making Tests A and B and the Inhibitory Control Test; biochemical markers for liver function and inflammatory processes and quality of life and nutritional responses.
Starting date	2010.
Contact information	Helen Vidot, Department Nutrition and Dietetics, RPAH, Camperdown NSW, Australia. Tel: + 61 2 9515 8053. Email: helen.vidot@sswahs.nsw.gov.au. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12610001021066.
Notes	Trial ID: ACTRN12610001021066. Still recruiting (February 2015).

BCAA: branched-chain amino acids.

DATA AND ANALYSES

Comparison 1. Branched-chain amino acids (BCAA) versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	15	760	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.69, 1.11]
2 Mortality: mode of administration	15	760	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.20]
2.1 Oral	8	363	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.63]
2.2 Intravenous	7	397	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.63, 1.28]
3 Mortality: type of hepatic encephalopathy	15	760	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.20]
3.1 Overt	11	563	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.61, 1.20]
3.2 Minimal	4	197	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.57, 2.38]
4 Mortality: type of control	15	783	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Placebo/no intervention	2	78	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.40, 1.37]
4.2 Isonitrogenous	4	230	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.80, 1.50]
4.3 Non-isonitrogenous	6	280	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.54, 1.53]
4.4 Lactulose	2	88	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.04, 2.08]
4.5 Neomycin	2	107	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.54, 2.84]
5 Mortality: type of data	15	760	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.20]
5.1 Re-calculated outcomes	4	255	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.47, 1.57]
5.2 Trial reports	11	505	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.65, 1.29]
6 Mortality: bias control	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Selection bias	10	521	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.70, 1.56]
6.2 Attrition bias	12	595	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.77, 1.27]
6.3 Reporting bias	15	760	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.20]
6.4 For-profit bias	12	621	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.68, 1.25]
6.5 Other bias	15	760	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.71, 1.20]
6.6 Combined bias assessment	8	437	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.65, 1.44]
7 Hepatic encephalopathy	16	827	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
8 Hepatic encephalopathy: mode of administration	16	827	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
8.1 Oral	9	430	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.52, 0.88]
8.2 Intravenous	7	397	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.61, 1.08]
9 Overt or minimal hepatic encephalopathy	16	827	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
9.1 Overt	12	630	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.58, 0.88]
9.2 Minimal	4	197	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.50, 1.12]
10 Hepatic encephalopathy: type of control	15	805	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.63, 0.90]
10.1 Placebo/no intervention	2	78	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.31, 1.91]
10.2 Isonitrogenous diet	5	350	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.57, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Non-isonitrogenous diet	4	182	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.49, 1.15]
10.4 Lactulose	2	88	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.48]
10.5 Neomycin	2	107	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.68]
11 Hepatic encephalopathy: type of data	16	827	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
11.1 Published data	12	572	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.62, 0.92]
11.2 Re-calculated based on unpublished data	4	255	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.34, 1.08]
12 Hepatic encephalopathy: publication status	16	827	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.62, 0.81]
12.1 Full-paper articles	15	760	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.63, 0.83]
12.2 Abstracts	1	67	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.48, 0.85]
13 Hepatic encephalopathy: bias control	16		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Selection bias	10	521	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.62, 0.97]
13.2 Performance and detection bias	8	450	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.59, 0.97]
13.3 Attrition bias	12	595	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.60, 0.92]
13.4 Reporting bias	12	595	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.60, 0.92]
13.5 For-profit bias	14	711	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.56, 0.86]
13.6 Other bias	16	827	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
13.7 Combined bias assessment	7	373	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.52, 0.96]
14 Hepatic encephalopathy: excluding 1 trial on people with or without cirrhosis	15	801	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
15 Hepatic encephalopathy: excluding trials with lactulose or neomycin controls	11	610	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.63, 0.92]
16 Hepatic encephalopathy: trials with lactulose or neomycin control	4	195	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.34, 1.30]
16.1 Lactulose	2	88	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.48]
16.2 Neomycin	2	107	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.68]
17 Nausea and diarrhoea	5	945	Risk Ratio (M-H, Random, 90% CI)	3.39 [0.70, 16.46]

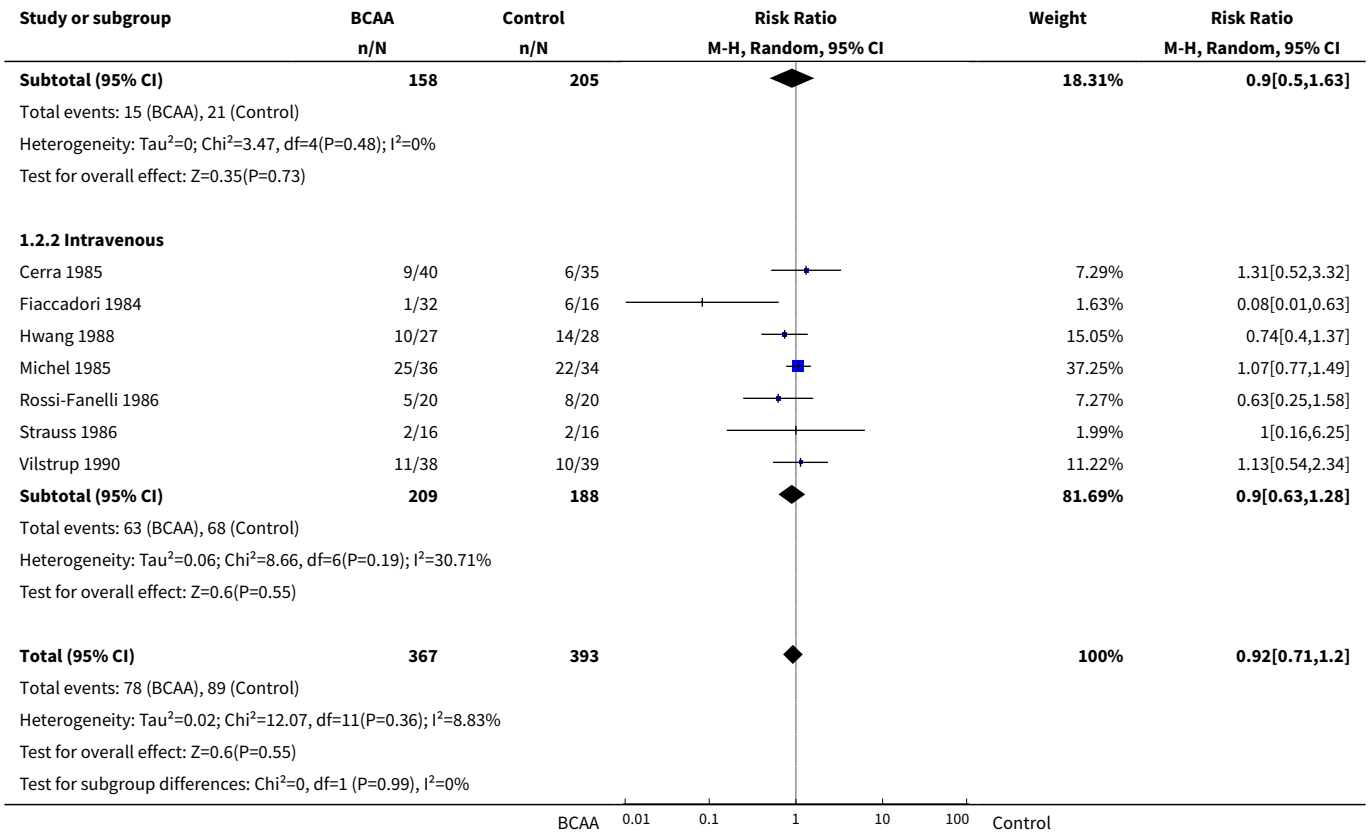
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Albumin	3	176	Mean Difference (IV, Random, 95% CI)	0.60 [-0.90, 2.09]
19 Nitrogen balance	3	108	Std. Mean Difference (IV, Random, 95% CI)	0.81 [0.07, 1.56]

Analysis 1.1. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 1 Mortality.

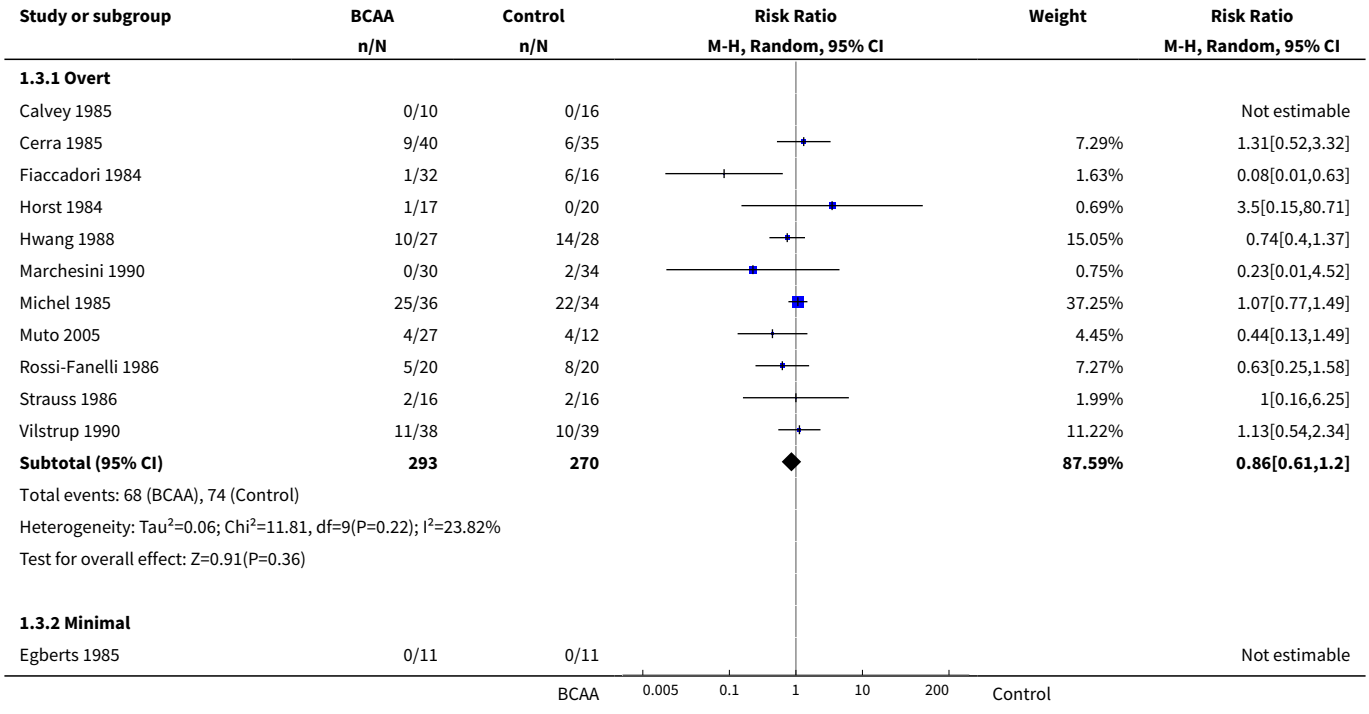
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Calvey 1985	0/10	0/16			Not estimable
Cerra 1985	9/40	6/35		7.14%	1.31[0.52,3.32]
Egberts 1985	0/11	0/11			Not estimable
Fiaccadori 1984	1/32	6/16		8.92%	0.08[0.01,0.63]
Horst 1984	1/17	0/20		0.51%	3.5[0.15,80.71]
Hwang 1988	10/27	14/28		15.32%	0.74[0.4,1.37]
Les 2011	5/18	6/22		6.02%	1.02[0.37,2.8]
Marchesini 1990	0/30	2/34		2.62%	0.23[0.01,4.52]
Marchesini 2003	5/33	9/79		5.91%	1.33[0.48,3.67]
Michel 1985	25/36	22/34		25.23%	1.07[0.77,1.49]
Muto 2005	4/27	4/12		6.17%	0.44[0.13,1.49]
Plauth 1993	0/12	0/11			Not estimable
Rossi-Fanelli 1986	5/20	8/20		8.92%	0.63[0.25,1.58]
Strauss 1986	2/16	2/16		2.23%	1[0.16,6.25]
Vilstrup 1990	11/38	10/39		11%	1.13[0.54,2.34]
Total (95% CI)	**367**	**393**		**100%**	**0.88[0.69,1.11]**
Total events: 78 (BCAA), 89 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.07, df=11(P=0.36); I^2=8.83%					
Test for overall effect: Z=1.07(P=0.28)					

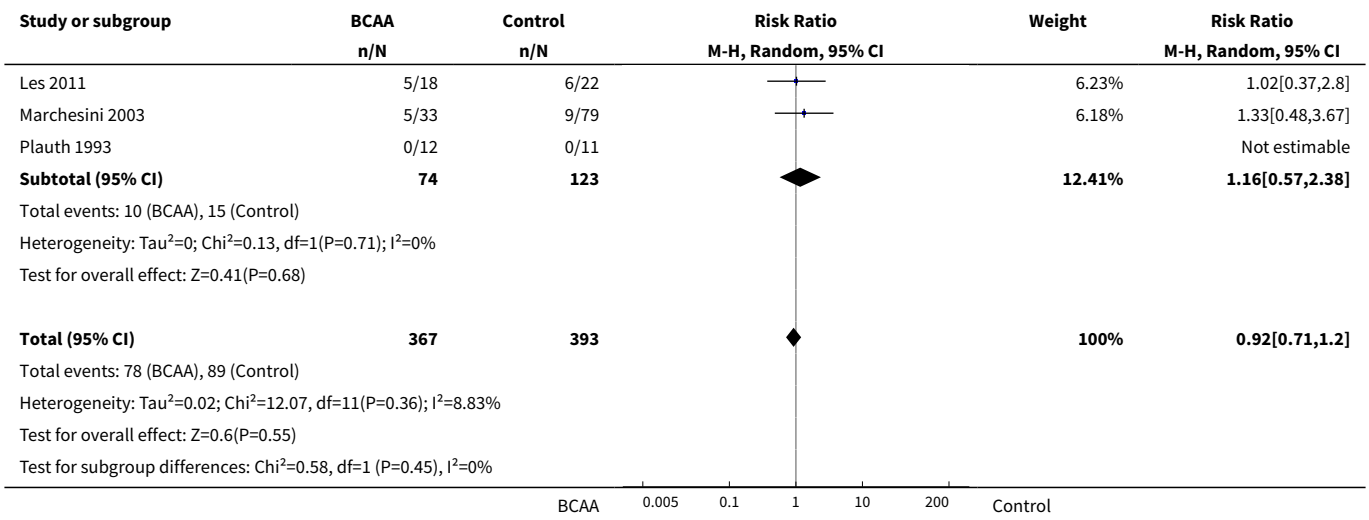
Analysis 1.2. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 2 Mortality: mode of administration.

Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Oral					
Calvey 1985	0/10	0/16			Not estimable
Egberts 1985	0/11	0/11			Not estimable
Horst 1984	1/17	0/20		0.69%	3.5[0.15,80.71]
Les 2011	5/18	6/22		6.23%	1.02[0.37,2.8]
Marchesini 1990	0/30	2/34		0.75%	0.23[0.01,4.52]
Marchesini 2003	5/33	9/79		6.18%	1.33[0.48,3.67]
Muto 2005	4/27	4/12		4.45%	0.44[0.13,1.49]
Plauth 1993	0/12	0/11			Not estimable

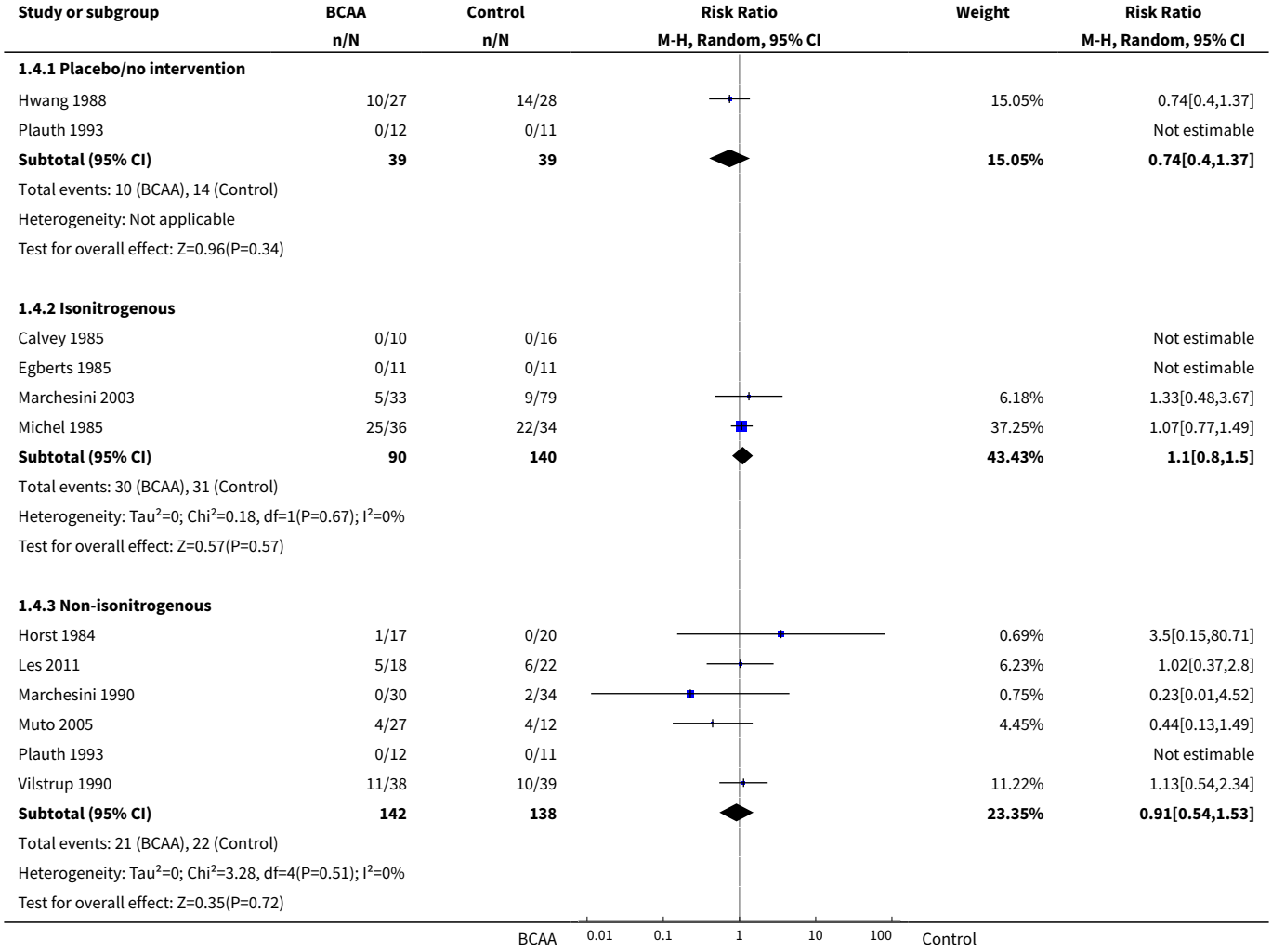


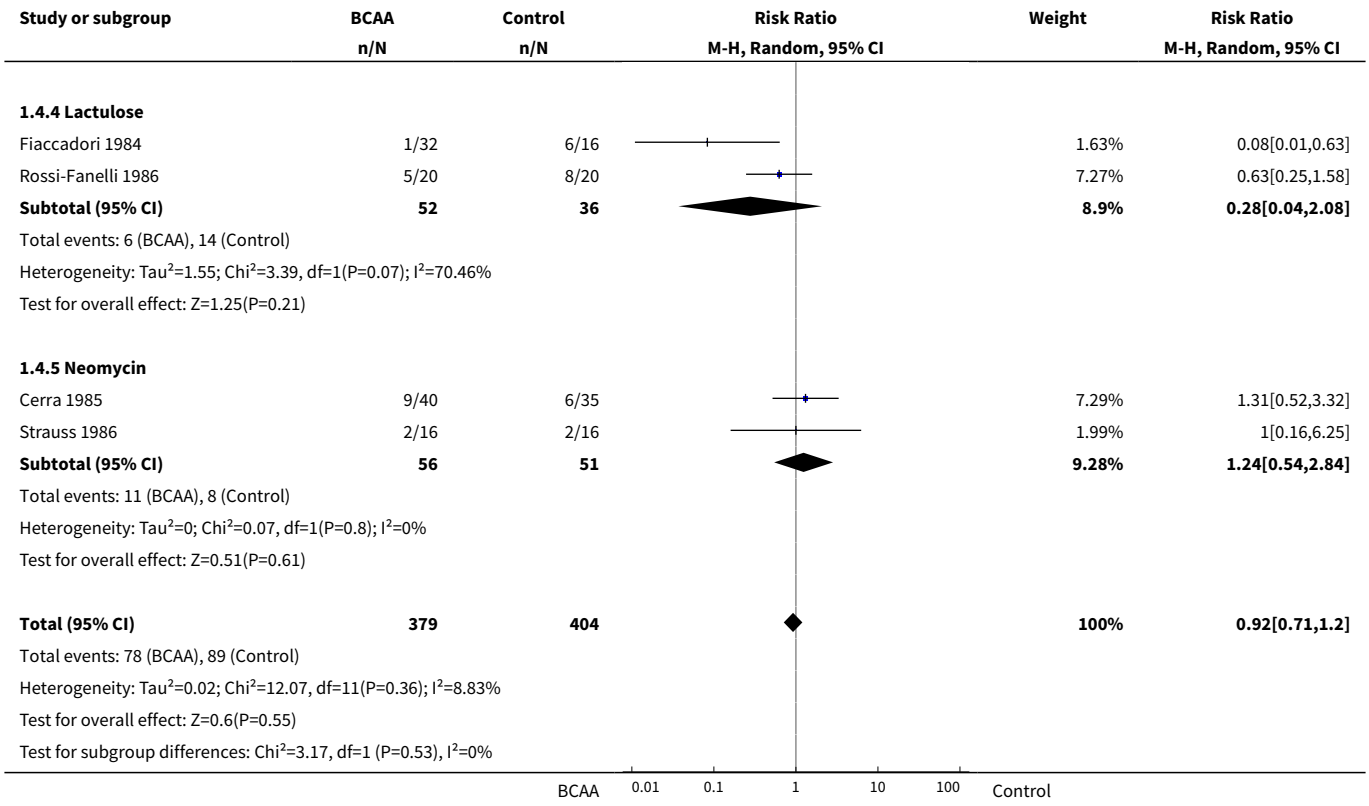
Analysis 1.3. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 3 Mortality: type of hepatic encephalopathy.



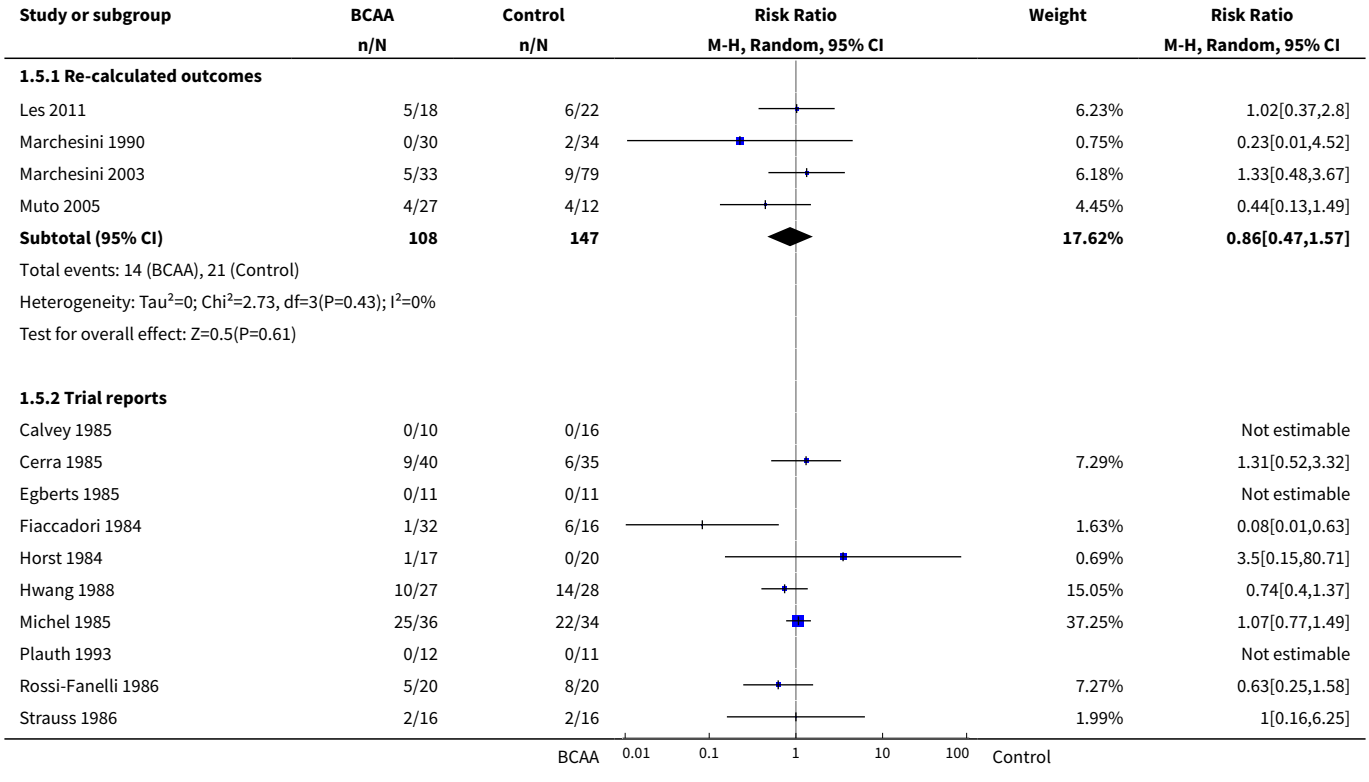


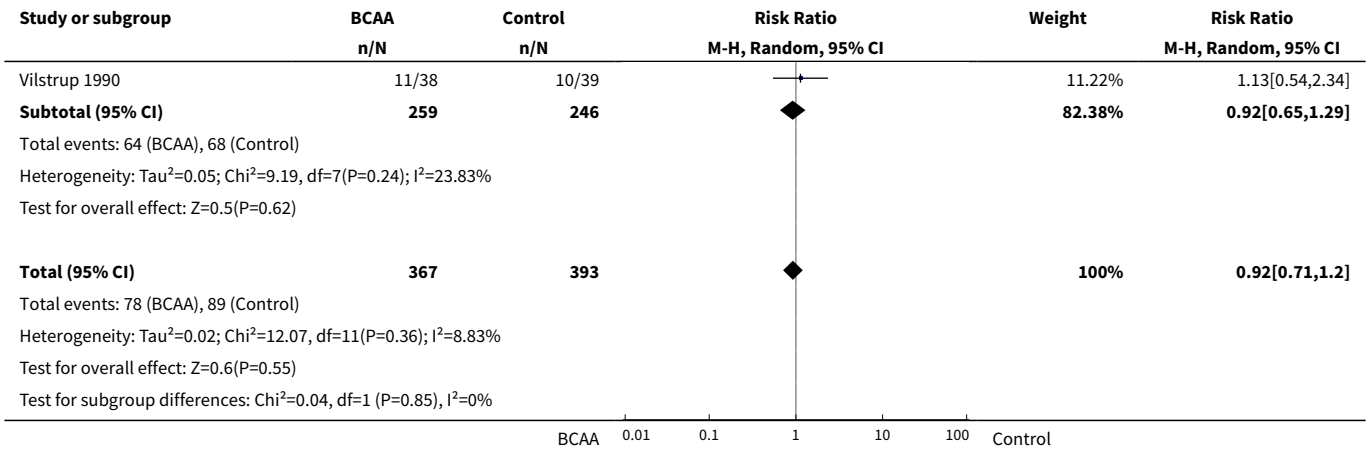
Analysis 1.4. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 4 Mortality: type of control.



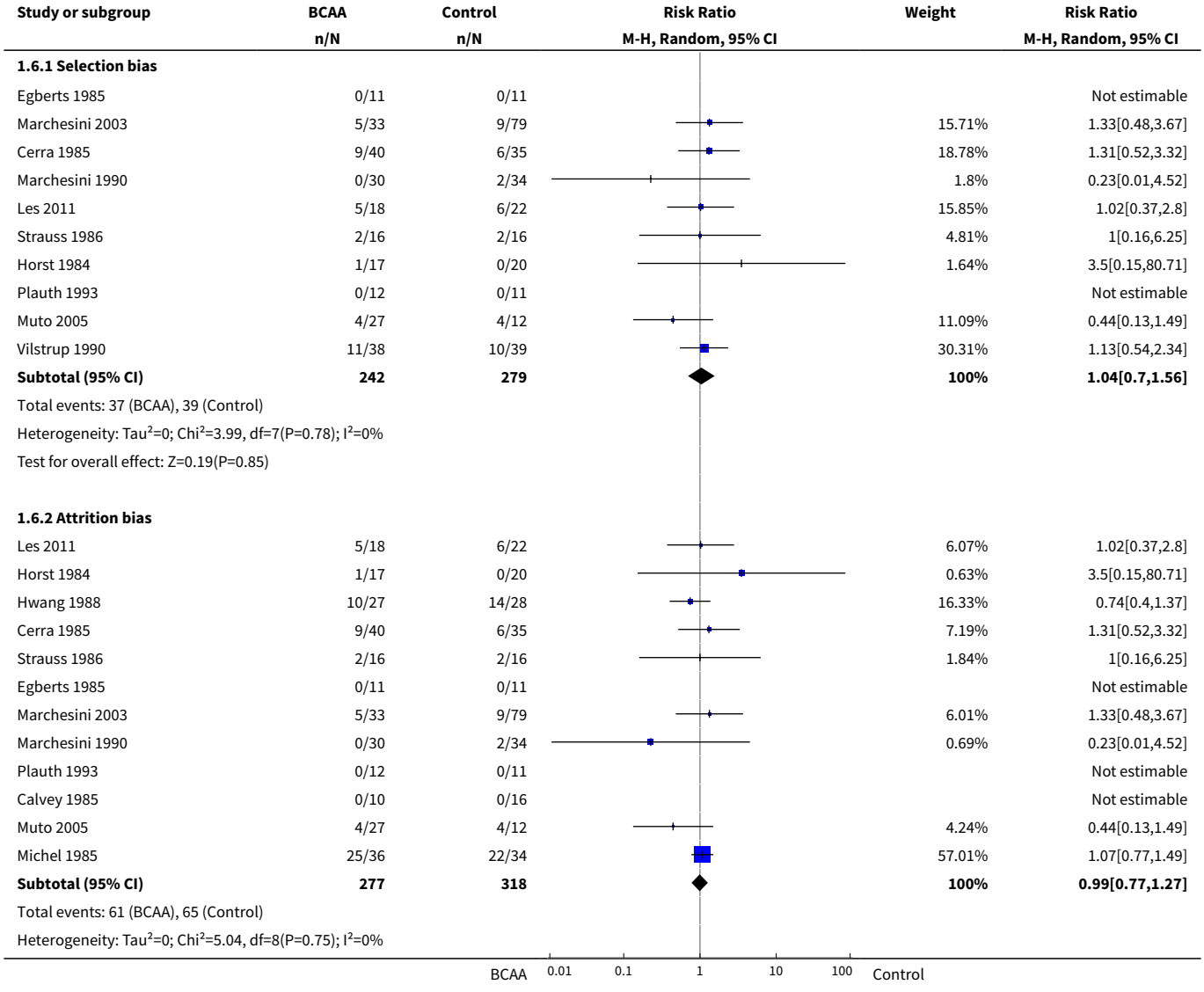


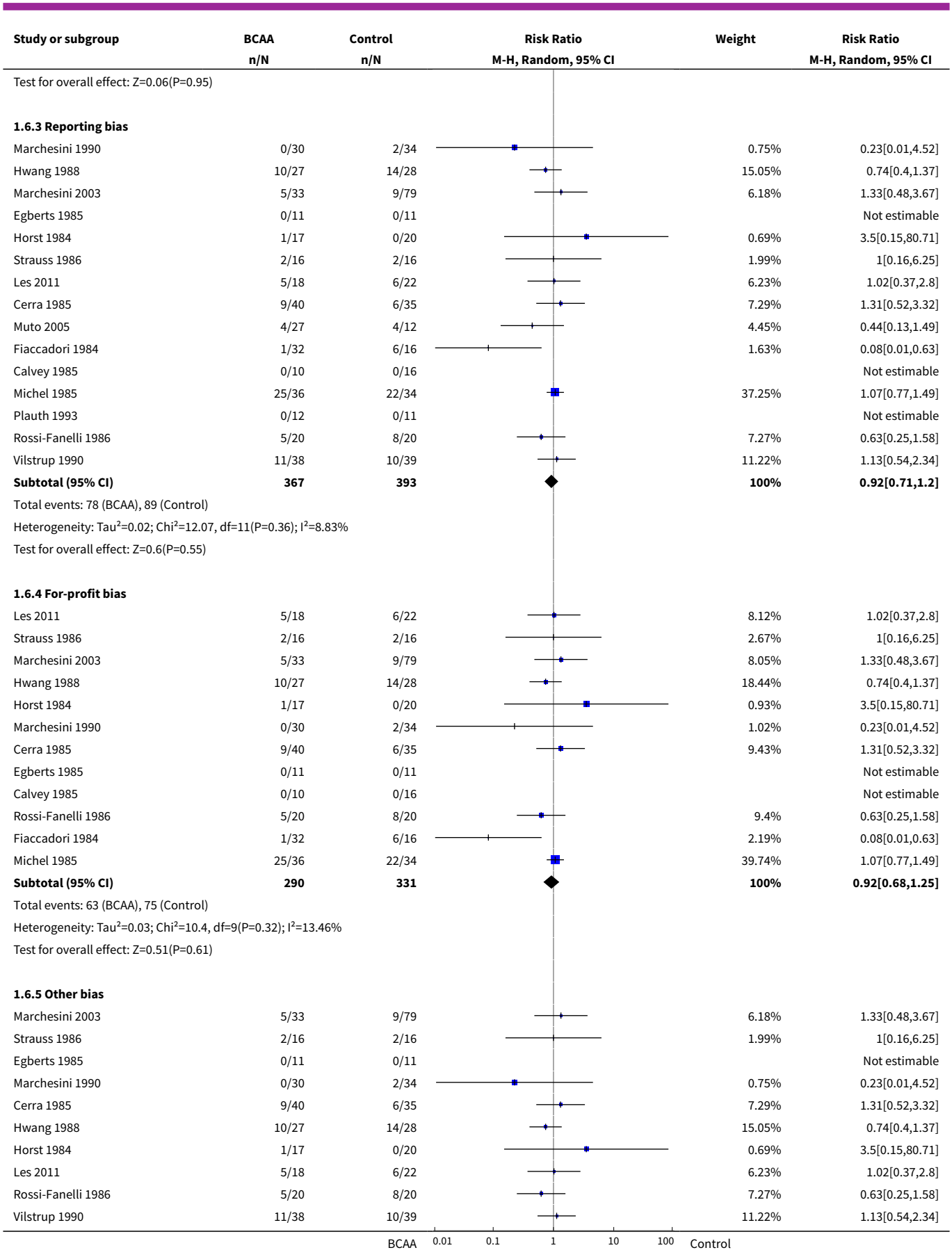
Analysis 1.5. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 5 Mortality: type of data.

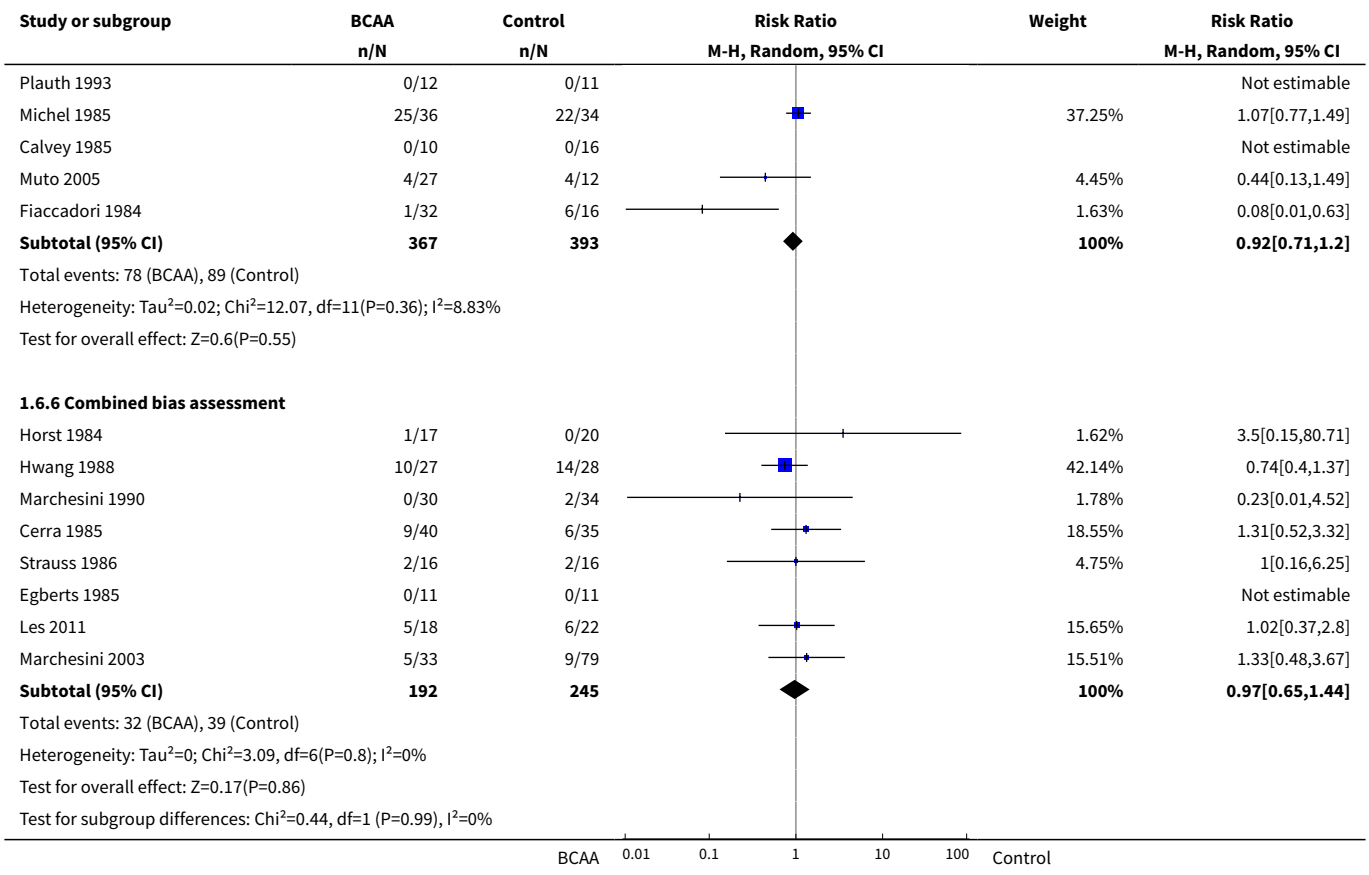




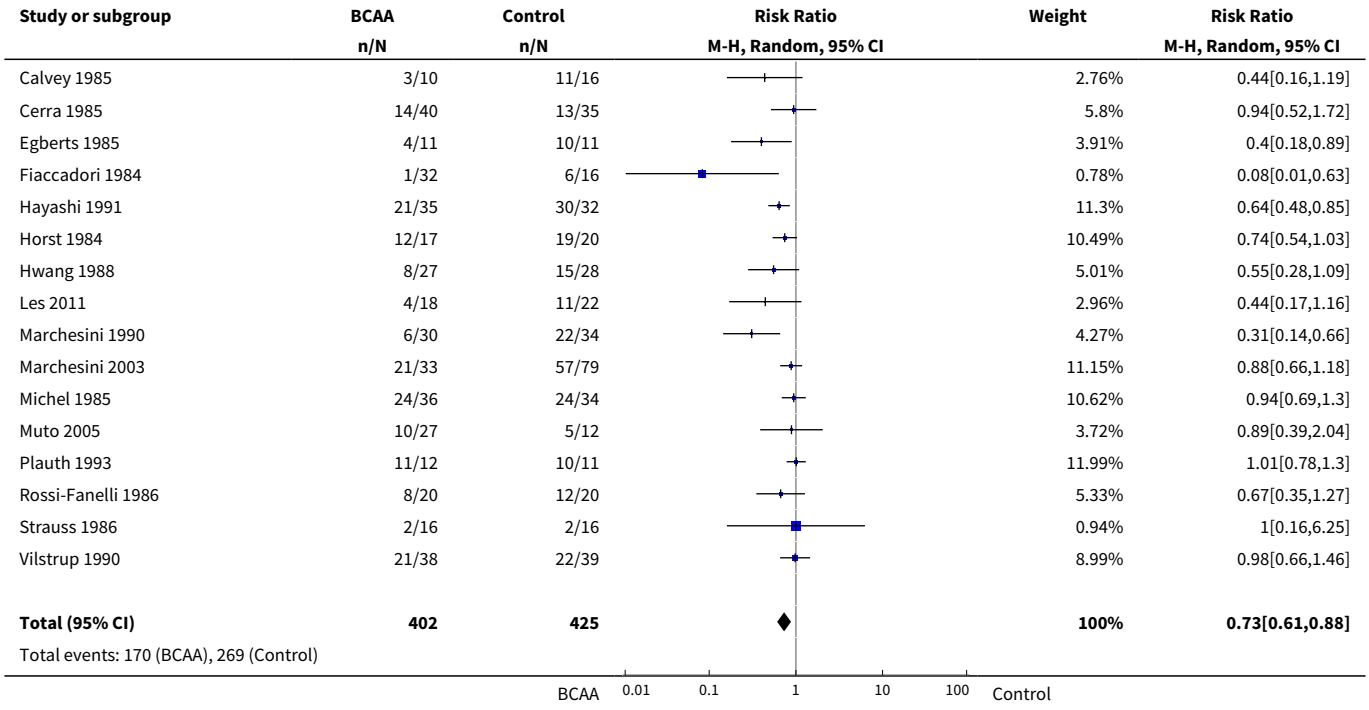
Analysis 1.6. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 6 Mortality: bias control.



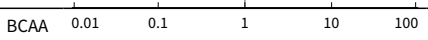




Analysis 1.7. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 7 Hepatic encephalopathy.



Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.06; Chi²=30.31, df=15(P=0.01); I²=50.51%					
Test for overall effect: Z=3.35(P=0)					



Analysis 1.8. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 8 Hepatic encephalopathy: mode of administration.

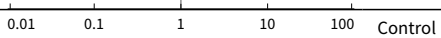
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Oral					
Calvey 1985	3/10	11/16		2.76%	0.44[0.16,1.19]
Egberts 1985	4/11	10/11		3.91%	0.4[0.18,0.89]
Hayashi 1991	21/35	30/32		11.3%	0.64[0.48,0.85]
Horst 1984	12/17	19/20		10.49%	0.74[0.54,1.03]
Les 2011	4/18	11/22		2.96%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		4.27%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		11.15%	0.88[0.66,1.18]
Muto 2005	10/27	5/12		3.72%	0.89[0.39,2.04]
Plauth 1993	11/12	10/11		11.99%	1.01[0.78,1.3]
Subtotal (95% CI)	**193**	**237**		**62.54%**	**0.67[0.52,0.88]**
Total events: 92 (BCAA), 175 (Control)					
Heterogeneity: Tau²=0.08; Chi²=22.51, df=8(P=0); I²=64.46%					
Test for overall effect: Z=2.94(P=0)					
1.8.2 Intravenous					
Cerra 1985	14/40	13/35		5.8%	0.94[0.52,1.72]
Fiaccadori 1984	1/32	6/16		0.78%	0.08[0.01,0.63]
Hwang 1988	8/27	15/28		5.01%	0.55[0.28,1.09]
Michel 1985	24/36	24/34		10.62%	0.94[0.69,1.3]
Rossi-Fanelli 1986	8/20	12/20		5.33%	0.67[0.35,1.27]
Strauss 1986	2/16	2/16		0.94%	1[0.16,6.25]
Vilstrup 1990	21/38	22/39		8.99%	0.98[0.66,1.46]
Subtotal (95% CI)	**209**	**188**		**37.46%**	**0.81[0.61,1.08]**
Total events: 78 (BCAA), 94 (Control)					
Heterogeneity: Tau²=0.04; Chi²=8.82, df=6(P=0.18); I²=31.96%					
Test for overall effect: Z=1.45(P=0.15)					
Total (95% CI)	**402**	**425**		**100%**	**0.73[0.61,0.88]**
Total events: 170 (BCAA), 269 (Control)					
Heterogeneity: Tau²=0.06; Chi²=30.31, df=15(P=0.01); I²=50.51%					
Test for overall effect: Z=3.35(P=0)					
Test for subgroup differences: Chi²=0.92, df=1 (P=0.34), I²=0%					

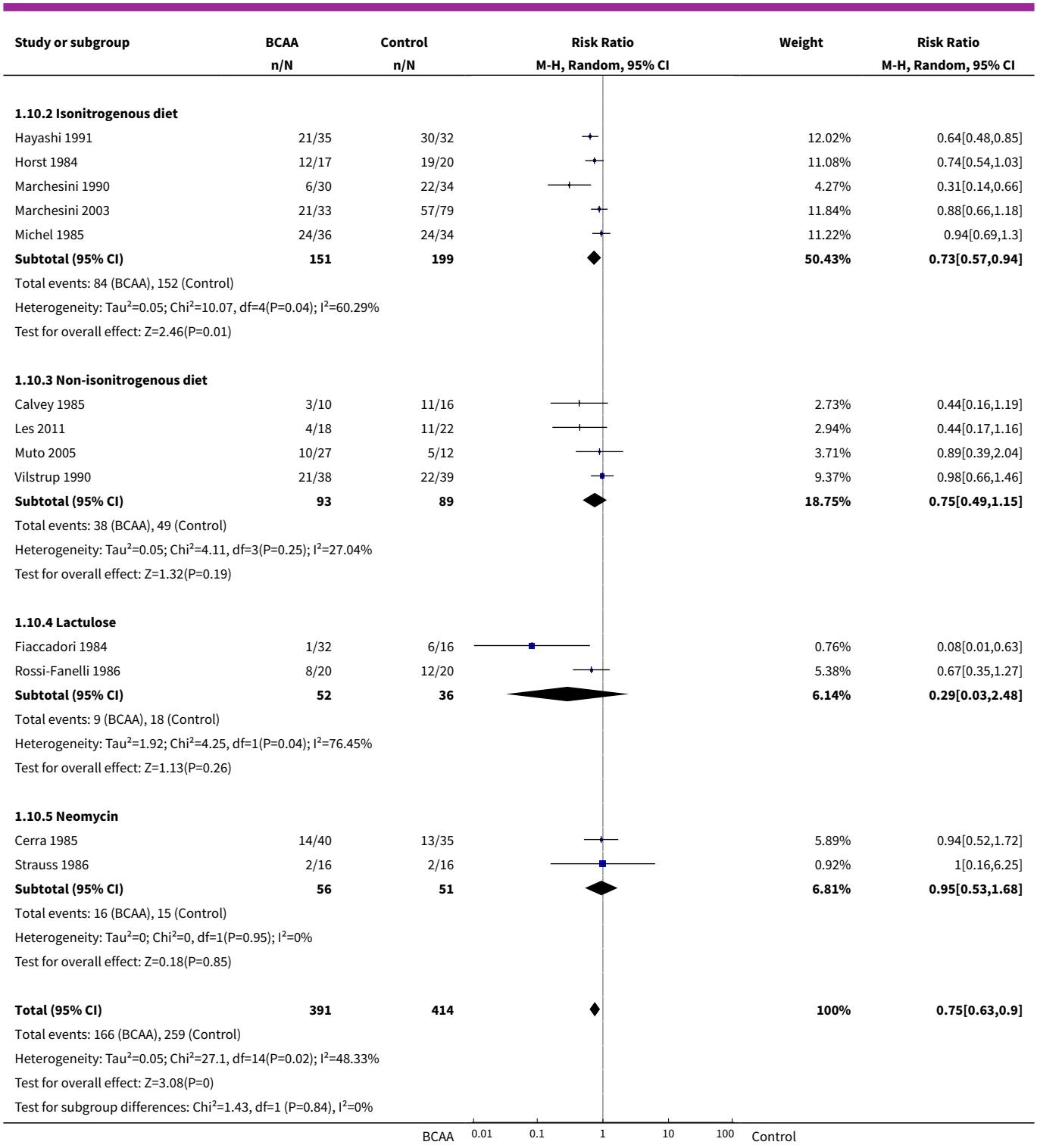
Analysis 1.9. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 9 Overt or minimal hepatic encephalopathy.

Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Overt					
Calvey 1985	3/10	11/16		2.76%	0.44[0.16,1.19]
Cerra 1985	14/40	13/35		5.8%	0.94[0.52,1.72]
Fiaccadori 1984	1/32	6/16		0.78%	0.08[0.01,0.63]
Hayashi 1991	21/35	30/32		11.3%	0.64[0.48,0.85]
Horst 1984	12/17	19/20		10.49%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		5.01%	0.55[0.28,1.09]
Marchesini 1990	6/30	22/34		4.27%	0.31[0.14,0.66]
Michel 1985	24/36	24/34		10.62%	0.94[0.69,1.3]
Muto 2005	10/27	5/12		3.72%	0.89[0.39,2.04]
Rossi-Fanelli 1986	8/20	12/20		5.33%	0.67[0.35,1.27]
Strauss 1986	2/16	2/16		0.94%	1[0.16,6.25]
Vilstrup 1990	21/38	22/39		8.99%	0.98[0.66,1.46]
Subtotal (95% CI)	**328**	**302**		**69.99%**	**0.71[0.58,0.88]**
Total events: 130 (BCAA), 181 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=18.41, df=11(P=0.07); I^2=40.26%					
Test for overall effect: Z=3.18(P=0)					
1.9.2 Minimal					
Egberts 1985	4/11	10/11		3.91%	0.4[0.18,0.89]
Les 2011	4/18	11/22		2.96%	0.44[0.17,1.16]
Marchesini 2003	21/33	57/79		11.15%	0.88[0.66,1.18]
Plauth 1993	11/12	10/11		11.99%	1.01[0.78,1.3]
Subtotal (95% CI)	**74**	**123**		**30.01%**	**0.75[0.5,1.12]**
Total events: 40 (BCAA), 88 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=9.47, df=3(P=0.02); I^2=68.32%					
Test for overall effect: Z=1.4(P=0.16)					
Total (95% CI)	**402**	**425**		**100%**	**0.73[0.61,0.88]**
Total events: 170 (BCAA), 269 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=30.31, df=15(P=0.01); I^2=50.51%					
Test for overall effect: Z=3.35(P=0)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%					

Analysis 1.10. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 10 Hepatic encephalopathy: type of control.

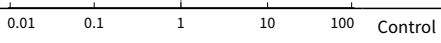
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Placebo/no intervention					
Hwang 1988	8/27	15/28		5.05%	0.55[0.28,1.09]
Plauth 1993	11/12	10/11		12.83%	1.01[0.78,1.3]
Subtotal (95% CI)	**39**	**39**		**17.87%**	**0.77[0.31,1.91]**
Total events: 19 (BCAA), 25 (Control)					
Heterogeneity: Tau^2=0.36; Chi^2=6.38, df=1(P=0.01); I^2=84.31%					
Test for overall effect: Z=0.56(P=0.58)					





Analysis 1.11. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 11 Hepatic encephalopathy: type of data.

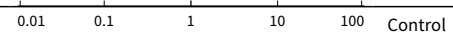
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Published data					
Calvey 1985	3/10	11/16		2.76%	0.44[0.16,1.19]
Cerra 1985	14/40	13/35		5.8%	0.94[0.52,1.72]
Egberts 1985	4/11	10/11		3.91%	0.4[0.18,0.89]
Fiaccadori 1984	1/32	6/16		0.78%	0.08[0.01,0.63]
Hayashi 1991	21/35	30/32		11.3%	0.64[0.48,0.85]
Horst 1984	12/17	19/20		10.49%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		5.01%	0.55[0.28,1.09]
Michel 1985	24/36	24/34		10.62%	0.94[0.69,1.3]
Plauth 1993	11/12	10/11		11.99%	1.01[0.78,1.3]
Rossi-Fanelli 1986	8/20	12/20		5.33%	0.67[0.35,1.27]
Strauss 1986	2/16	2/16		0.94%	1[0.16,6.25]
Vilstrup 1990	21/38	22/39		8.99%	0.98[0.66,1.46]
Subtotal (95% CI)	**294**	**278**		**77.91%**	**0.76[0.62,0.92]**
Total events: 129 (BCAA), 174 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=20.74, df=11(P=0.04); I^2=46.97%					
Test for overall effect: Z=2.75(P=0.01)					
1.11.2 Re-calculated based on unpublished data					
Les 2011	4/18	11/22		2.96%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		4.27%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		11.15%	0.88[0.66,1.18]
Muto 2005	10/27	5/12		3.72%	0.89[0.39,2.04]
Subtotal (95% CI)	**108**	**147**		**22.09%**	**0.61[0.34,1.08]**
Total events: 41 (BCAA), 95 (Control)					
Heterogeneity: Tau^2=0.22; Chi^2=8.9, df=3(P=0.03); I^2=66.29%					
Test for overall effect: Z=1.7(P=0.09)					
Total (95% CI)	**402**	**425**		**100%**	**0.73[0.61,0.88]**
Total events: 170 (BCAA), 269 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=30.31, df=15(P=0.01); I^2=50.51%					
Test for overall effect: Z=3.35(P=0)					
Test for subgroup differences: Chi^2=0.51, df=1 (P=0.47), I^2=0%					



Analysis 1.12. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 12 Hepatic encephalopathy: publication status.

Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 Full-paper articles					
Calvey 1985	3/10	11/16		3.44%	0.44[0.16,1.19]
Cerra 1985	14/40	13/35		5.64%	0.94[0.52,1.72]
Egberts 1985	4/11	10/11		4.07%	0.4[0.18,0.89]
Fiaccadori 1984	1/32	6/16		3.26%	0.08[0.01,0.63]
Horst 1984	12/17	19/20		7.11%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		5.99%	0.55[0.28,1.09]

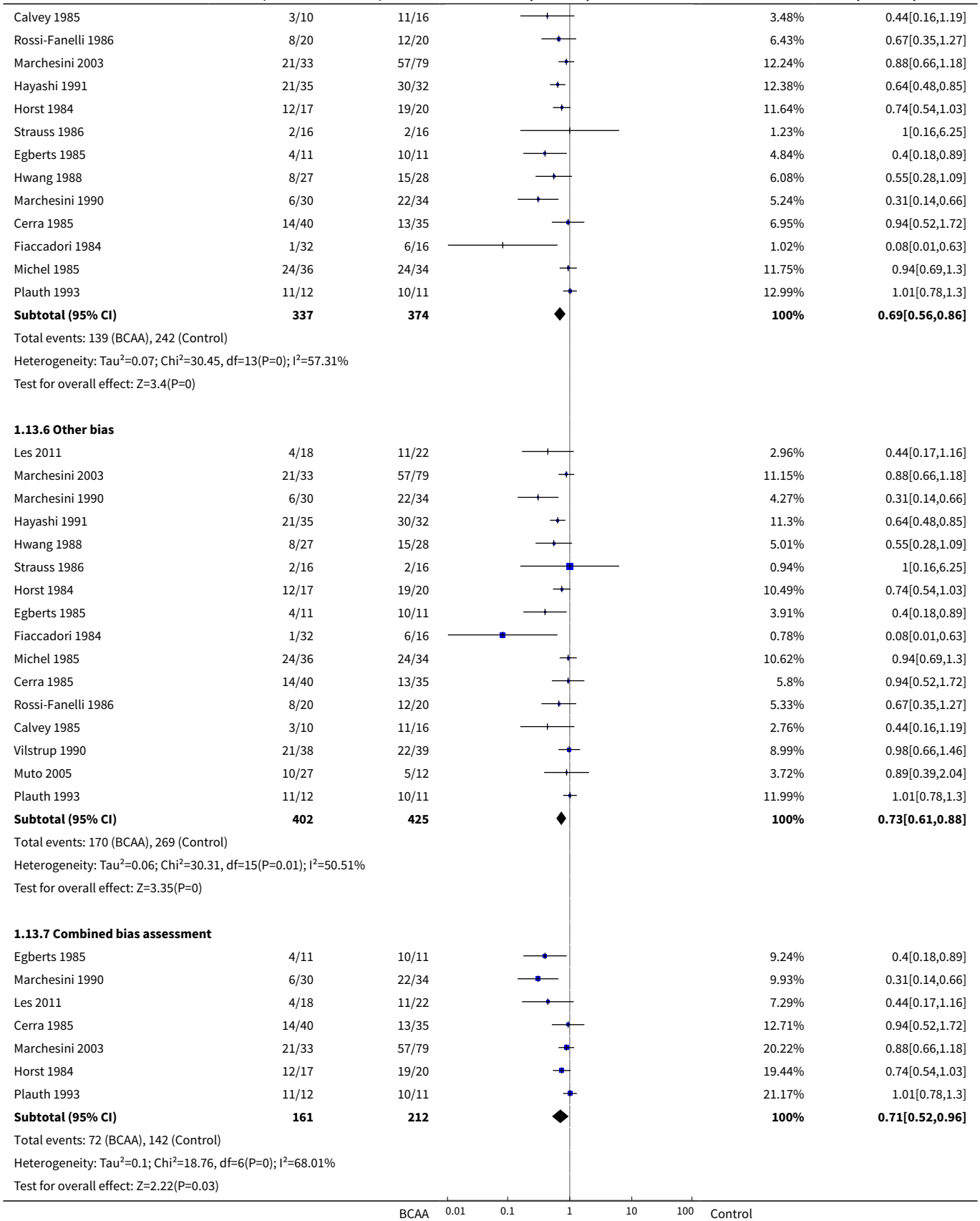
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Les 2011	4/18	11/22		4.03%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		8.39%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		13.67%	0.88[0.66,1.18]
Michel 1985	24/36	24/34		10.05%	0.94[0.69,1.3]
Muto 2005	10/27	5/12		2.82%	0.89[0.39,2.04]
Plauth 1993	11/12	10/11		4.25%	1.01[0.78,1.3]
Rossi-Fanelli 1986	8/20	12/20		4.88%	0.67[0.35,1.27]
Strauss 1986	2/16	2/16		0.81%	1[0.16,6.25]
Vilstrup 1990	21/38	22/39		8.84%	0.98[0.66,1.46]
Subtotal (95% CI)	**367**	**393**		**87.24%**	**0.72[0.63,0.83]**
Total events: 149 (BCAA), 239 (Control)					
Heterogeneity: Tau^2=0; Chi^2=28.77, df=14(P=0.01); I^2=51.33%					
Test for overall effect: Z=4.62(P<0.0001)					
1.12.2 Abstracts					
Hayashi 1991	21/35	30/32		12.76%	0.64[0.48,0.85]
Subtotal (95% CI)	**35**	**32**		**12.76%**	**0.64[0.48,0.85]**
Total events: 21 (BCAA), 30 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.07(P=0)					
Total (95% CI)	**402**	**425**		**100%**	**0.71[0.62,0.81]**
Total events: 170 (BCAA), 269 (Control)					
Heterogeneity: Tau^2=0; Chi^2=30.31, df=15(P=0.01); I^2=50.51%					
Test for overall effect: Z=5.28(P<0.0001)					
Test for subgroup differences: Chi^2=0.52, df=1 (P=0.47), I^2=0%					



Analysis 1.13. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 13 Hepatic encephalopathy: bias control.

Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Selection bias					
Strauss 1986	2/16	2/16		1.42%	1[0.16,6.25]
Egberts 1985	4/11	10/11		5.96%	0.4[0.18,0.89]
Horst 1984	12/17	19/20		16.47%	0.74[0.54,1.03]
Les 2011	4/18	11/22		4.5%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		6.52%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		17.55%	0.88[0.66,1.18]
Cerra 1985	14/40	13/35		8.93%	0.94[0.52,1.72]
Plauth 1993	11/12	10/11		18.95%	1.01[0.78,1.3]
Vilstrup 1990	21/38	22/39		14.02%	0.98[0.66,1.46]
Muto 2005	10/27	5/12		5.67%	0.89[0.39,2.04]
Subtotal (95% CI)	**242**	**279**		**100%**	**0.78[0.62,0.97]**
Total events: 105 (BCAA), 171 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=17.53, df=9(P=0.04); I^2=48.65%					
Test for overall effect: Z=2.19(P=0.03)					

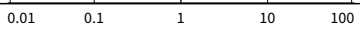
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.13.2 Performance and detection bias					
Egberts 1985	4/11	10/11		7.06%	0.4[0.18,0.89]
Marchesini 1990	6/30	22/34		7.67%	0.31[0.14,0.66]
Horst 1984	12/17	19/20		17.21%	0.74[0.54,1.03]
Marchesini 2003	21/33	57/79		18.12%	0.88[0.66,1.18]
Les 2011	4/18	11/22		5.44%	0.44[0.17,1.16]
Cerra 1985	14/40	13/35		10.19%	0.94[0.52,1.72]
Vilstrup 1990	21/38	22/39		15.06%	0.98[0.66,1.46]
Plauth 1993	11/12	10/11		19.26%	1.01[0.78,1.3]
Subtotal (95% CI)	**199**	**251**		**100%**	**0.76[0.59,0.97]**
Total events: 93 (BCAA), 164 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=17.9, df=7(P=0.01); I^2=60.9%					
Test for overall effect: Z=2.16(P=0.03)					
1.13.3 Attrition bias					
Les 2011	4/18	11/22		4.08%	0.44[0.17,1.16]
Michel 1985	24/36	24/34		14.34%	0.94[0.69,1.3]
Egberts 1985	4/11	10/11		5.37%	0.4[0.18,0.89]
Hwang 1988	8/27	15/28		6.85%	0.55[0.28,1.09]
Strauss 1986	2/16	2/16		1.3%	1[0.16,6.25]
Cerra 1985	14/40	13/35		7.93%	0.94[0.52,1.72]
Horst 1984	12/17	19/20		14.18%	0.74[0.54,1.03]
Calvey 1985	3/10	11/16		3.8%	0.44[0.16,1.19]
Marchesini 2003	21/33	57/79		15.04%	0.88[0.66,1.18]
Marchesini 1990	6/30	22/34		5.85%	0.31[0.14,0.66]
Muto 2005	10/27	5/12		5.11%	0.89[0.39,2.04]
Plauth 1993	11/12	10/11		16.14%	1.01[0.78,1.3]
Subtotal (95% CI)	**277**	**318**		**100%**	**0.74[0.6,0.92]**
Total events: 119 (BCAA), 199 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=22.03, df=11(P=0.02); I^2=50.07%					
Test for overall effect: Z=2.73(P=0.01)					
1.13.4 Reporting bias					
Cerra 1985	14/40	13/35		7.93%	0.94[0.52,1.72]
Strauss 1986	2/16	2/16		1.3%	1[0.16,6.25]
Marchesini 2003	21/33	57/79		15.04%	0.88[0.66,1.18]
Calvey 1985	3/10	11/16		3.8%	0.44[0.16,1.19]
Michel 1985	24/36	24/34		14.34%	0.94[0.69,1.3]
Horst 1984	12/17	19/20		14.18%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		6.85%	0.55[0.28,1.09]
Egberts 1985	4/11	10/11		5.37%	0.4[0.18,0.89]
Les 2011	4/18	11/22		4.08%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		5.85%	0.31[0.14,0.66]
Plauth 1993	11/12	10/11		16.14%	1.01[0.78,1.3]
Muto 2005	10/27	5/12		5.11%	0.89[0.39,2.04]
Subtotal (95% CI)	**277**	**318**		**100%**	**0.74[0.6,0.92]**
Total events: 119 (BCAA), 199 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=22.03, df=11(P=0.02); I^2=50.07%					
Test for overall effect: Z=2.73(P=0.01)					
1.13.5 For-profit bias					
Les 2011	4/18	11/22		3.73%	0.44[0.17,1.16]



Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.66, df=1 (P=1), I²=0%					

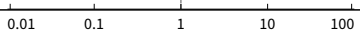
Analysis 1.14. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 14 Hepatic encephalopathy: excluding 1 trial on people with or without cirrhosis.

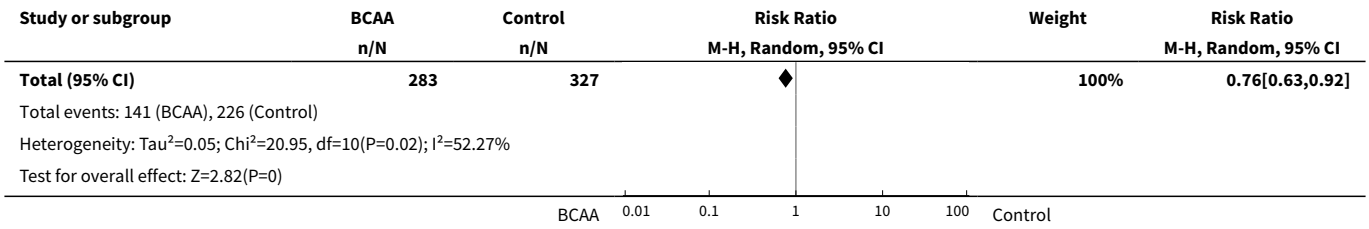
Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Cerra 1985	14/40	13/35		5.92%	0.94[0.52,1.72]
Egberts 1985	4/11	10/11		3.97%	0.4[0.18,0.89]
Fiaccadori 1984	1/32	6/16		0.78%	0.08[0.01,0.63]
Hayashi 1991	21/35	30/32		11.7%	0.64[0.48,0.85]
Horst 1984	12/17	19/20		10.84%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		5.1%	0.55[0.28,1.09]
Les 2011	4/18	11/22		3%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		4.34%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		11.53%	0.88[0.66,1.18]
Michel 1985	24/36	24/34		10.97%	0.94[0.69,1.3]
Muto 2005	10/27	5/12		3.78%	0.89[0.39,2.04]
Plauth 1993	11/12	10/11		12.43%	1.01[0.78,1.3]
Rossi-Fanelli 1986	8/20	12/20		5.43%	0.67[0.35,1.27]
Strauss 1986	2/16	2/16		0.95%	1[0.16,6.25]
Vilstrup 1990	21/38	22/39		9.25%	0.98[0.66,1.46]
Total (95% CI)	**392**	**409**		**100%**	**0.74[0.62,0.89]**
Total events: 167 (BCAA), 258 (Control)					
Heterogeneity: Tau²=0.05; Chi²=28.49, df=14(P=0.01); I²=50.86%					
Test for overall effect: Z=3.16(P=0)					



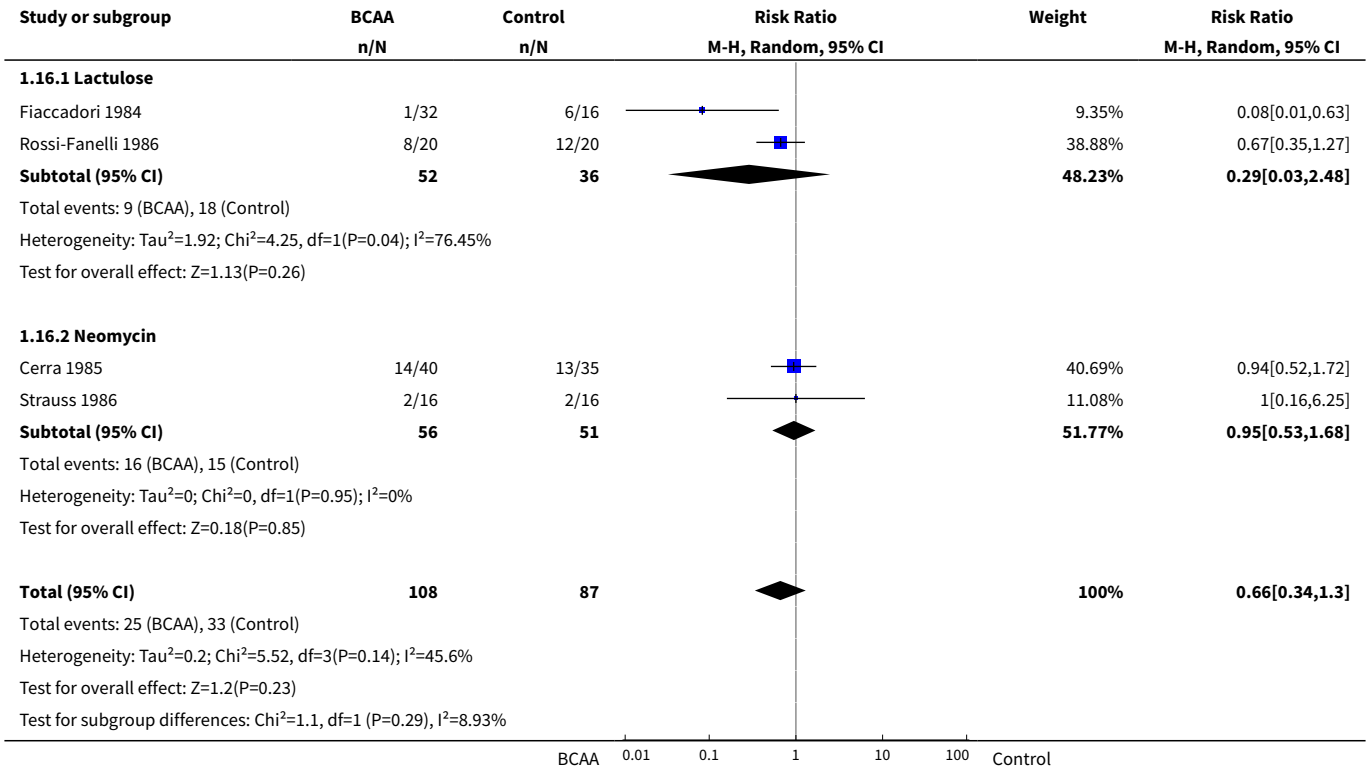
Analysis 1.15. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 15 Hepatic encephalopathy: excluding trials with lactulose or neomycin controls.

Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Calvey 1985	3/10	11/16		3.03%	0.44[0.16,1.19]
Hayashi 1991	21/35	30/32		13.95%	0.64[0.48,0.85]
Horst 1984	12/17	19/20		12.8%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		5.66%	0.55[0.28,1.09]
Les 2011	4/18	11/22		3.26%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		4.78%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		13.73%	0.88[0.66,1.18]
Michel 1985	24/36	24/34		12.97%	0.94[0.69,1.3]
Muto 2005	10/27	5/12		4.14%	0.89[0.39,2.04]
Plauth 1993	11/12	10/11		14.95%	1.01[0.78,1.3]
Vilstrup 1990	21/38	22/39		10.74%	0.98[0.66,1.46]

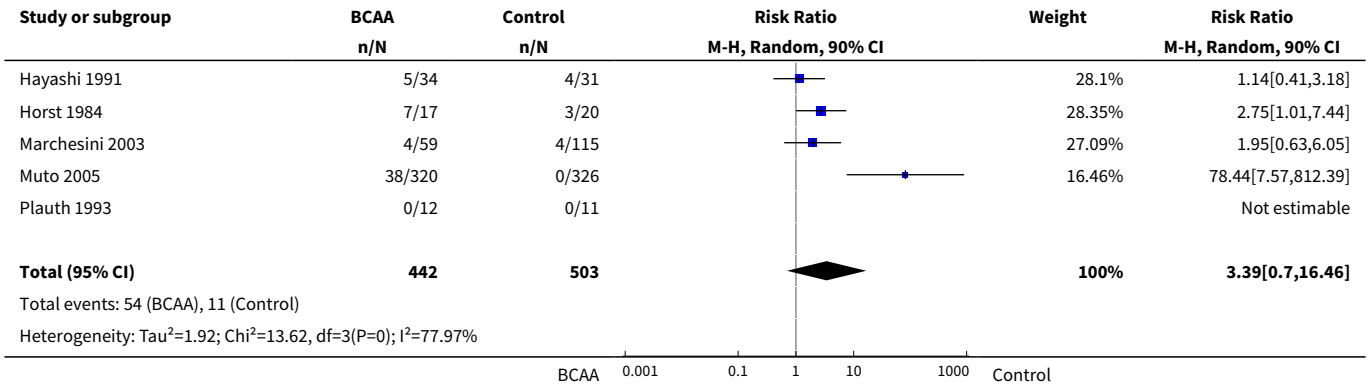


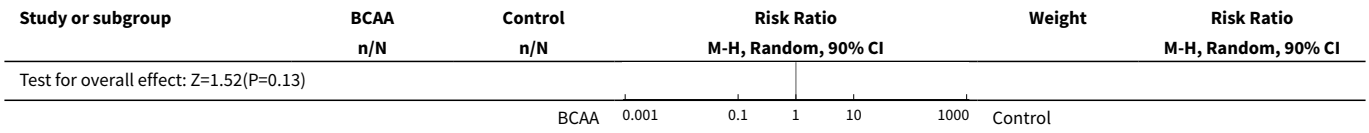


Analysis 1.16. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 16 Hepatic encephalopathy: trials with lactulose or neomycin control.

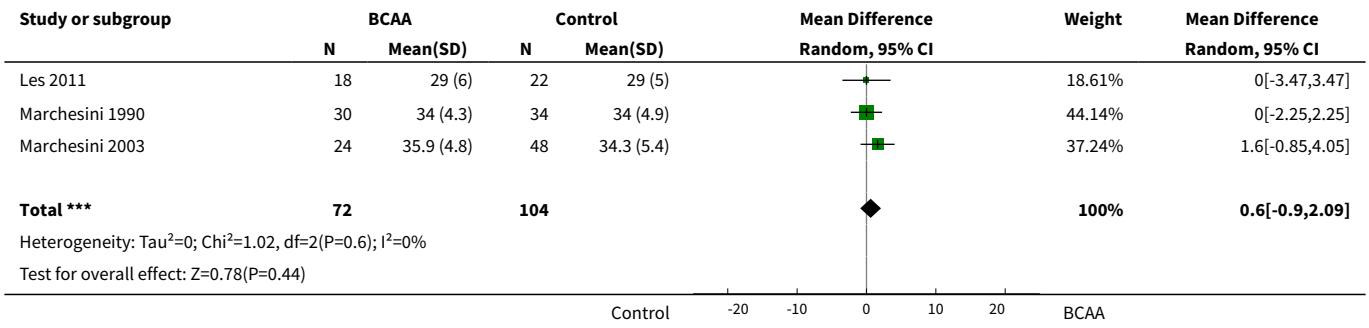


Analysis 1.17. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 17 Nausea and diarrhoea.

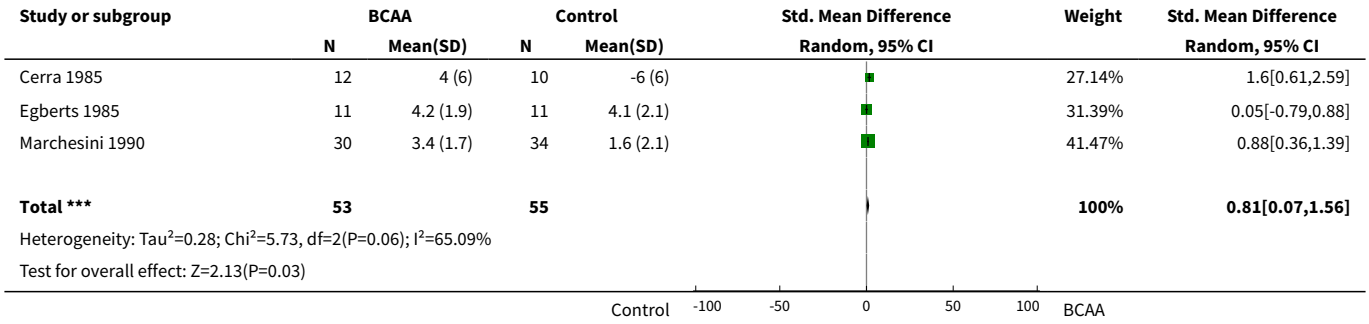




Analysis 1.18. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 18 Albumin.



Analysis 1.19. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 19 Nitrogen balance.



APPENDICES

Appendix 1. Search strategies

Database	Time span	Search terms
The Cochrane Hepato-Biliary Group Controlled Trials Register	May 2017.	branched-chain AND (encephalopath* OR liver disease* OR cirrho*)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Issue 4 of 12, 2017.	#1 MeSH descriptor: [Amino Acids, Branched-Chain] explode all trees #2 branched chain #3 #1 or #2

(Continued)

		#4 MeSH descriptor: [Hepatic Encephalopathy] explode all trees #5 MeSH descriptor: [Liver Diseases] explode all trees #6 MeSH descriptor: [Fibrosis] explode all trees #7 encephalopath* or liver disease* or cirrho* #8 #4 or #5 or #6 or #7 #9 #3 and #8
MEDLINE Ovid	1946 to May 2017.	1. exp Amino Acids, Branched-Chain/ 2. branched chain.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 3. 1 or 2 4. exp Hepatic Encephalopathy/ 5. exp Liver Diseases/ 6. exp Fibrosis/ 7. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 8. 4 or 5 or 6 or 7 9. 3 and 8 10. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 11. 9 and 10
Embase Ovid	1974 to May 2017.	1. exp branched chain amino acid/ 2. branched chain.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 3. 1 or 2 4. exp hepatic encephalopathy/ 5. exp liver disease/ 6. exp fibrosis/ 7. (encephalopath* or liver disease* or cirrho*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 8. 4 or 5 or 6 or 7 9. 3 and 8 10. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 11. 9 and 10
Science Citation Index Expanded and	1900 to May 2017.	#5 #4 AND #3

(Continued)

Conference Proceedings Citation Index – Science (Web of Science)		#4 TS=(random* or blind* or placebo* or meta-analysis) #3 #2 AND #1 #2 TS=(encephalopath* or liver disease* or cirrho*) #1 TS=branched chain
Lilacs (Bireme)	1982 to May 2017	aminoacid$ OR (amino acid$) [Words] and (encephalopath$ OR liver disease$ OR cirrho$) [Words]

FEEDBACK

*Downgrading of the quality of evidence due to imprecision, 29 July 2015

Summary

We received a suggestion to downgrade the quality of the evidence for the outcome 'nausea and diarrhoea' based on imprecision.

Reply

We agree with the comment and have downgraded the evidence.

Contributors

Lise Lotte Gluud incorporated the change.

WHAT'S NEW

Date	Event	Description
4 March 2020	Amended	Clarification message from the Co-ordinating Editor added to the Declarations of interest statement about the review's compliance with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy.

HISTORY

Protocol first published: Issue 1, 1997
Review first published: Issue 2, 2003

Date	Event	Description
5 May 2017	New search has been performed	New search conducted.
5 May 2017	New citation required but conclusions have not changed	No additional trials identified.

CONTRIBUTIONS OF AUTHORS

Lise Lotte Gluud and Hendrik Vilstrup reviewed and updated the methods based on the previous review with incorporation of the revised guidelines described in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Lise Lotte Gluud, Gitte Dam, Iñigo Les, Giulio Marchesini, Mette Borre, Niels Kristian Aagaard, and Hendrik Vilstrup approved of the final version of the manuscript.

DECLARATIONS OF INTEREST

None of the authors have any financial interests that may conflict with this review.

Lise Lotte Gluud had previously conducted Cochrane systematic reviews on the treatment of hepatic encephalopathy. As explained in the Cochrane Hepato-Biliary Group module (Gluud 2017), this entails a risk of academic bias. Lise Lotte Gluud participated in scientific meetings in Denmark sponsored by Norgine.
Giulio Marchesini, Iñigo Les, and Hendrik Vilstrup had previously conducted clinical trials on BCAA, which also entails a risk of academic bias.
Niels Kristian Aagaard, Gitte Dam, and Mette Borre have no conflicts of interest.

Post-publication declaration of interest

Clarification statement added from the CHBG Co-ordinating Editor on 04.03.2020: This review was found by the Cochrane Funding Arbiters, post-publication, to be noncompliant with the Cochrane conflict of interest policy, which includes the relevant parts of the Cochrane Commercial Sponsorship Policy. It will be updated by 04.03.2021. The update will have a majority of authors and lead author free of conflicts.

SOURCES OF SUPPORT

Internal sources

- No funding, Other.

External sources

- No funding, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The methods of the review were updated to reflect the current guidelines described in the *Cochrane Handbook for Systematic Reviews of Interventions* and the Cochrane Hepato-Biliary Group Module. Based on the most recent recommendations, the primary outcomes were mortality, hepatic encephalopathy, and adverse events. We also updated the assessment of bias control and statistical analyses. The previous review included published data from trials with a high proportion of people with hepatic encephalopathy at baseline. We were able to retrieve data that allowed re-calculation of outcomes and were, therefore, able to limit our analyses to people with hepatic encephalopathy. Accordingly, we did not evaluate the proportion of people with hepatic encephalopathy in our trial selection criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Amino Acids, Branched-Chain [adverse effects] [*therapeutic use]; Bias; Diarrhea [etiology]; Hepatic Encephalopathy [*drug therapy] [mortality]; Injections, Intravenous; Nausea [etiology]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male